U.S. FOOD & DRUG ADMINISTRATION

2022

Advancing Regulatory Science at FDA:

FOCUS AREAS OF REGULATORY SCIENCE (FARS)


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The FDA is a complex organization with a regulatory mission that is fulfilled in the context of public health, policy, law and science. While public health, policy, and law are very much in the public view, the deep and broad scientific base of the FDA is not so apparent and at times is under-appreciated. This report highlights updates to the 2021 FDA's Focus Areas of Regulatory Science and makes apparent the incredible breadth and depth of FDA's science base.

This report provides fascinating insight into the multidimensional spectrum of our science remit. The complexity of the human condition, including biology, physical sciences, social factors, environment and behavior is addressed by FDA's detailed work on special populations, including children, racial and ethnic minorities and women. The range of products from food to cosmetics, supplements, drugs, devices, biologics (in people and animals) and tobacco makes the case that multiple areas of science must be brought together in order to derive optimal regulatory decisions.

Undergirding the scientific enterprise is this convergence of sciences as the universe is increasingly described in digital form, enabling previously unfathomable sources of data to be brought together. Consider the need to determine safe levels of a contaminant in food, the implications of a change in the microbial patterns in animals to human health or the likely risk of changes in software in complex medical devices. Resolution of such issues requires expertise in special areas of science combined with teamwork across disciplines.

In addition to highlighting the diverse scientific areas that must be brought to bear on regulatory decisions, this document should convince any potential skeptics that the FDA cannot do its job without extensive scientific collaboration. The academic world is an important source of collaboration, as are the industries that develop and manufacture products regulated by FDA. As we work together to define the underlying science, regulations and guidance are developed to establish standards and approaches, respectively, to meeting regulatory requirements. Often gaps in scientific understanding are identified that make developing such standards difficult or impossible. Most of the scientific activities described in this report have been undertaken by FDA to fill in such scientific voids in order to develop appropriate regulatory standards and recommended approaches. When making specific product decisions, FDA must independently and impartially assess whether the product or process meets the established regulatory standards. Thus, the science described in this report is both a public good and the basis for specific regulatory actions.

Accordingly, amidst all this scientific splendor, the definition of scientific facts and principles must lead to standard operations that enable the FDA to make decisions in the face of uncertainty, while also propelling continued knowledge generation that is not proprietary to any specific product and serves as a common framework for the FDA and the regulated industry. This is the nature of regulatory science.

We want to take this opportunity to thank Dr. Jacqueline O'Shaughnessy for her excellent work as Acting Chief Scientist. She has led this far-reaching organization with grace and a deep knowledge base as evidenced in this update to the 2021 report, which happened under her leadership.

We are delighted that Dr. O'Shaughnessy is staying on as Deputy for the Office of the Chief Scientist as we welcome Dr. Namandjé Bumpus as our new Chief Scientist. As we contemplated the future of the FDA's science mission and its leader, we dreamed of a person like Dr. Bumpus. She is an accomplished scientist, leading a laboratory focused on infectious disease pharmacology and proteomics at the level of a single cell. She is also a seasoned administrator, with a variety of leadership roles at Johns Hopkins, including her position as Chair of the Department of Pharmacology and Molecular Sciences and the EK Marshall and Thomas H Maren Professor in Pharmacology. In addition to all of her academic achievements, she is an enthusiastic proponent for public health. As she deals with the complex internal world and the federal, academic and industry scientific communities, she will be an extraordinarily powerful leader. And together, Drs. Bumpus and O'Shaughnessy will be an ideal team to advance our mission across the broad spectrum reflected in this 2022 report.

OPENING STATEMENT FROM THE CHIEF SCIENTIST

Namandjé N. Bumpus

Jacqueline A. O'Shaughnessy

Chief Scientist Dr. Namandjé N. Bumpus and Deputy Chief Scientist Dr. Jacqueline A. O'Shaughnessy

Every day, FDA research scientists address regulatory challenges to provide scientific and objective data, tools, and expertise to support evaluation of FDA-regulated products. As an agency, we are committed to making important regulatory decisions that use sound science and data. We do this by performing intramural research and scientific activities, collaborating with stakeholders in the scientific community, and harnessing the best science to ensure that we have the expertise and resources to improve processes, inform decision-making, and enable innovation in support of FDA's mission.

A key purpose of the *Focus Areas of Regulatory Science (FARS)* is to communicate the importance and impact of FDA's cross-cutting on-going regulatory science research activities on a regulator basis. Because we aim to stay ahead of evolving regulatory needs, we have reviewed each of the FARS from the 2021 report and provided important updates to the examples highlighted in the FARS. The ability to stay agile with regular updating ensures that the FARS include the most current topics and examples of FDA's regulatory science to fulfill our regulatory responsibilities.

Additionally, we aim to advance regulatory science in several cross-cutting areas. In the 2021 report, we identified priorities in women's health, minority health, health equity across diverse groups, and the One Health initiative. In 2022, we bolstered our cross-cutting topics to include pediatric health, rare diseases, and oncology. Lastly, we continue to emphasize that the FARS are not intended to be a comprehensive list of all FDA areas of regulatory science and recognize there are many on-going efforts and initiatives at the Agency that are not included in this report. Center- and office-specific research outside of the current FARS are no less important than the identified FARS.

We are proud to highlight these achievements of our scientists, supporting our mission to protect and advance public health by helping to speed innovations in regulatory science. And the Office of the Chief Scientist will continue to support FDA's centers and offices as we partner with the broader scientific community to advance regulatory science, research, and innovation as we aim to harness the vast potential of rapidly evolving technologies in support of FDA's mission.

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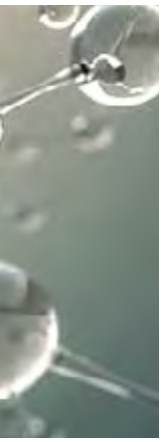
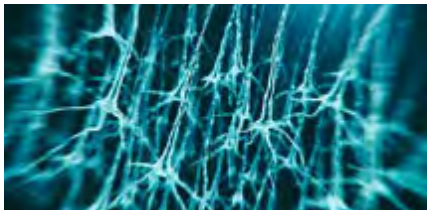




Overview

The United States (U.S.) Department of Health and Human Services (HHS), Food and Drug Administration (FDA) regulates and oversees a broad range of products used by the American public every day, from human and animal food, cosmetics, and tobacco, to medical products, such as drugs, biologics, and medical devices. Together, FDA's multi-disciplinary workforce of **approximately 18,000 employees** supports the oversight of FDA-regulated products. **FDA is responsible** for oversight of more than **$2.8 trillion** of food, medical products, cosmetics, and tobacco, accounting for roughly **20 cents of every dollar** spent by U.S. consumers.

The health and well-being of the American public depend on FDA's science-based regulatory decisions. Under the authority of Congress, FDA creates rules and regulations based on the laws set forth in the **Federal Food, Drug, and Cosmetic Act (FD&C Act, Public Law 97-414)**, and other laws, to fulfill its **public health mission**. FDA scientists conduct **regulatory science** to create data, tools, models, and methods to facilitate evaluation or development of FDA-regulated products as well as to support regulatory decision-making and policy development.

Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of some FDA-regulated products.

While industry mainly focuses on product development and academia focuses on the scientific underpinnings, FDA, in addition to its other activities, conducts or supports regulatory science research that concentrates on developing test methods, models and knowledge of the science needed to support regulatory evaluation.

Regulatory science is essential because it enables FDA to understand and assess risks, prepare for public health emergencies, and ultimately help ensure the safety or reduce the harm of products used or consumed by the public. FDA does this by providing scientific, non-biased, and objective expertise for the products under FDA's jurisdiction. Our use of regulatory science supports FDA's mission in a variety of ways, like developing assays, animal models, data analysis tools, scientifically sound guidance, and reference materials or standards used by FDA in the regulatory process and sponsors developing FDA-regulated products. Moreover, output from regulatory science supports education by sharing best practices through guidance with national and international stakeholders; supports regulatory decision-making through marketing authorization decisions, regulations, consumer advisories, labeling, industry warnings, and recalls.

Approach

In 2020, FDA formed an Agency-wide committee of scientific leaders to develop an efficient way to communicate to its stakeholders its regulatory science needs and activities. The committee surveyed the Agency's working groups, councils, and research teams, and developed the report ***Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS)***. The intention of the report was to communicate areas FDA identified as needing continued targeted investment to fulfill FDA's regulatory and public health **mission**. The format is designed to easily accommodate frequent updates and revisions to align with the rapid pace of scientific advancement as well as evolving priorities and research activities.

Each focus area section follows the same format: a description of why the focus area is important to FDA and examples of recent and ongoing research. In 2021, the main updates were to the examples, although minor updates were also made to the importance statements of some of the focus areas.

We continue to emphasize that the FARS are not intended to be a comprehensive list of all FDA areas of regulatory science and recognize there are many efforts and initiatives on-going at the Agency that are not included here. Center- and office-specific research outside of the current FARS are no less important than the identified FARS. Additionally, some of the research FDA conducts is preliminary in nature, and inclusion in FARS does not necessarily imply any determination about use for or role in regulatory decision-making.

The FARS are organized across four initiatives established in 2020:

- Public Health Emergency Preparedness and Response
- Increasing Choice and Competition through Innovation
- Unleashing the Power of Data
- Empowering Patients and Consumers

FARS-related research is conducted through a variety of mechanisms and collaborations, such as intramural and extramural regulatory science programs identified by FDA centers and offices. This report also highlights the Research Capabilities, Tools, and Resources available that centers and offices utilize when performing any regulatory science research. That section includes descriptions of:

- Research Management and Collaborations
- Scientific Education, Training, and Communication
- Infrastructure

Cross-cutting Topics

In developing the FARS, FDA determined that certain topics encompass multiple focus areas because of broad application. As such, FDA identified the following cross-cutting topics underlying much of FDA's regulatory science research: Minority Health and Health Equity, Women's Health, Pediatric Health, Oncology, **Rare Diseases** and the One Health Initiative. Moreover, additional consideration was given to describing the lifecycle of FDA-regulated products; the committee included details for how FARS can influence different aspects of that lifecycle.

The **Coronavirus Disease 2019 (COVID-19)** pandemic is central to many of the research examples listed in the FARS. COVID-19 is a contagious respiratory disease caused by infection with a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In 2020, FDA initiated an ongoing **rapid response** to the pandemic including conducting regulatory evaluations of medical products used to diagnose, treat, or prevent COVID-19, and developed new research programs to facilitate development and regulatory evaluation of these critical **medical countermeasures**.

Minority Health and Health Equity Regulatory Science Research

FDA's **Office of Minority Health and Health Equity** (OMHHE) leads efforts to advance minority health and health equity- focused regulatory science research. To support research efforts, OMHHE engages across all FDA product centers and offices, as well as a broad range of stakeholders, including academia, minority-serving institutions, government agencies, and non-profit organizations.

OMHHE leverages various funding mechanisms, collaborations, and partnerships to advance its mission by establishing new scientific initiatives and supporting novel health disparity and health equity-focused intramural and extramural research. The OMHHE Challenge Grants support intramural research in collaboration with FDA scientists. The OMHHE extramural research

OMHHE Mission

The FDA Office of Minority Health and Health Equity (OMHHE) works to promote and protect the health of diverse populations through research and communication that addresses health disparities. OMHHE serves as the principal advisor to the Commissioner and other key officials on scientific and policy issues relating to the health of racial and ethnic minorities, and other underrepresented or underserved populations. OMMHE advocates, collaborates, and partners within and outside FDA for the participation of racial and ethnic minorities, and other diverse populations in clinical trials. OMHHE also supports activities to expand language access.

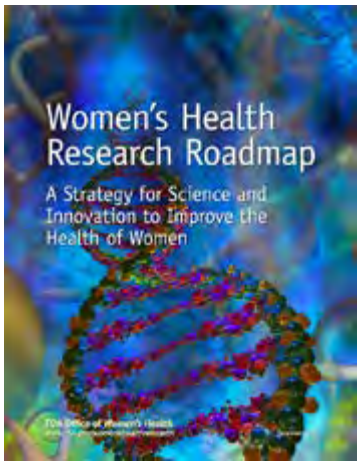
program supports extramural research in collaboration with diverse organizations through OMHHE Innovation Award grants, the Broad Agency Announcements, the Centers of Excellence in Regulatory Science and Innovation, Research Collaboration Agreements, and Inter-Agency Agreements.

OMHHE advances regulatory science by supporting research that contributes to the reduction of health disparities and advancement of health equity. For example, supporting research that contributes to advancing inclusion of racial and ethnic minority populations in clinical trials, and the continued evaluation of FDA regulated products by demographic data including, but not limited to, ethnicity, race, age, and geography.

OMHHE also advances scientific workforce diversity by supporting post-doctoral fellowship programs such as the Genomic Science and Health Equity (GSHE) Postdoctoral Fellowship, a joint program with the FDA OMHHE and the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH).

Women's Health Regulatory Science Research

Women's Health Research is a critical element in regulatory science because medical products can affect men and women differently. FDA's Office of Women's Health (OWH) sets the Agency's research agenda for women and funds research and development activities related to advancing the science of women's health and sex and gender differences. OWH collaborates across FDA to identify priority topic areas to create OWH's **Women's Health Research Roadmap**. The Office focuses funding on cross-cutting research within FDA centers to expand existing research projects and foster new collaborations. In addition, OWH works with other governmental agencies, academia, women's research organizations, and other stakeholders to facilitate research projects and scientific forums to advance FDA's understanding of women's health and the impact of sex and gender differences on health, disease, and medicine. OWH's work advances regulatory science through the development of new tools and approaches to inform FDA decisions about the safety, effectiveness, or reduction of associated harms of FDA-regulated products that are used not only by women, but by all Americans.



OWH awards intramural research grants and extramural funding through the **Advancing Regulatory Science Broad Agency Announcement** and **Centers of Excellence in Regulatory Science and Innovation** programs. The programs support **regulatory science research** that addresses knowledge gaps in sex and gender differences in product safety and effectiveness, and women's health concerns related to FDA-regulated therapeutic products. OWH funds research that concerns health issues affecting women across their lifespan, including cardiovascular disease, breast cancer, medical device and nutritional supplement safety, pregnancy and lactation, and reproductive health. In addition, OWH

OWH Mission

The FDA Office of Women's Health (OWH) serves as the principal advisor to the Commissioner and other key Agency officials on scientific, ethical, and policy issues relating to women's health. OWH coordinates efforts to establish and advance a women's health agenda for the Agency, promotes the inclusion of women in clinical trials and the implementation of guidelines concerning the representation of women in clinical trials and the completion of sex/gender analysis. OWH also identifies and monitors emerging women's health needs, and serves as the Agency's liaison with other agencies, industry, professional associations and advocacy groups with regards to the health of women.

OWH achieves its mission through the foundational principle that sex as a biological variable should be factored into research design, analysis, reporting and education. To this end, OWH supports FDA's regulatory mission by engaging in scientific research and collaborating with stakeholders to engage in scientific and educational projects. These initiatives are coordinated through research and development, education, and public outreach.

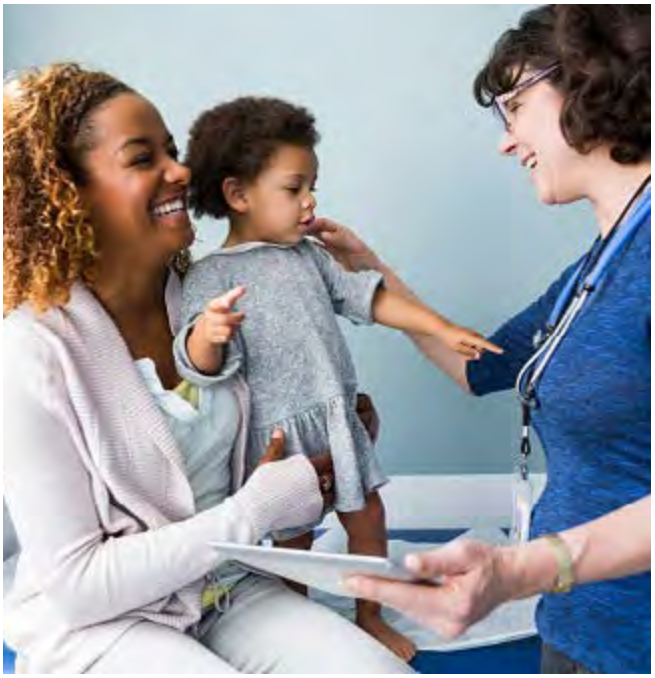
works across government agencies and with external stakeholders to advocate for research inclusion and real-world data collection to inform and improve the safety of FDA-regulated products used during pregnancy and lactation. Results from OWH-supported research have led to safety-related labeling changes, product development guidance for industry, and new evidence-based communications about FDA-regulated products used by pregnant and lactating **individuals**. Learn more about **women's health regulatory science research**.

Maternal Health Regulatory Science Research

Pregnant and lactating individuals have historically been underrepresented in research. However, the COVID-19 pandemic has highlighted the importance of studying these populations to inform the safety, dosing, and effectiveness of products regulated by FDA. The Division of Pediatrics and Maternal Health (DPMH) in the Office of New Drugs also engages in regulatory science research to address challenges related to maternal health issues, especially related to collection of data that can support improved data and communication of pregnancy and lactation data in prescription drug product labeling. Like the work in pediatrics, DPMH in collaboration with internal and external experts, publishes papers in scientific journals that advance areas of important data collection during pregnancy and lactation, with a focus on safety data collection. A primary focus of DPMH's regulatory science research in maternal health involves research questions to address the optimal communication of risk information in the pregnancy and lactation sections of prescription drug product labeling. Other areas of active interest in DPMH's maternal health regulatory science research involve use of modeling tools (e.g., physiological based pharmacokinetic modeling) to predict dosing of drugs that may be used during pregnancy, examination of recent trends in drug and supplement utilization during pregnancy and lactation, assessment of drug concentration in breastmilk for certain drugs, understanding neonatal enzyme ontogeny and its influence on drug exposure via breastmilk, and risk management of teratogens. Additionally, the Office of Surveillance and Epidemiology (OSE) and DPMH have been actively participating in collaborative research to evaluate pregnancy outcomes related to COVID-19 as a collaborator in the COVID-19 Infection and Medicines in Pregnancy (CONSIGN) project established by the European Medicines Agency. OSE is also leading projects to better understand the capabilities of Sentinel's linked mother-infant data to enhance safety data collection for drugs used during pregnancy.

Maternal Health Regulatory Science Research

Alongside OWH, The Office of New Drugs also engages in regulatory science research to address challenges related to maternal health issues, especially related to collection of data that can support improved data and communication of pregnancy and lactation data in prescription drug product labeling.



Pediatric Health Regulatory Science Research

The FDA is committed to addressing scientific and regulatory issues unique to therapeutics development in children including leveraging of existing data to facilitate efficient and successful pediatric drug development programs.

Moreover, the Division of Pediatrics and Maternal Health (DPMH) in the Office of New Drugs engages in regulatory science research to address challenges in pediatric drug development, especially with development of therapeutics targeting rare pediatric diseases. DPMH, in collaboration with other Divisions and disciplines

Pediatric Health Regulatory Science Research

The Office of Pediatric Therapeutics is mandated to help ensure children have access to innovative, safe and effective medical products. They also coordinate and facilitate activities, across the FDA, that may have any effect on a pediatric population, the practice of pediatrics, or involve pediatric issues.

at the FDA, publishes papers in scientific journals that advance pediatric therapeutics development. A primary focus of DPMH's regulatory science research in pediatrics involves research questions to address specific challenges encountered in the development of drugs for pediatric patients, including extrapolation of efficacy, use of complex innovative trial designs, application of biomarkers and surrogate endpoints, predicting and analyzing clinical pharmacology information in children, developing clinical trial endpoints, safety assessment, and analysis of negative trials. Additionally, DPMH has access to a large database of clinical trial data from over 1,600 pediatric clinical trials that can be used to address these challenges. DPMH establishes pediatric research collaborations using many effective mechanisms, including research collaboration agreements, memoranda of understanding, and Broad Agency Announcements. Moreover, the Division leverages innovative tools, including crowdsourcing challenges, to engage external stakeholders in identifying regulatory science research questions that can advance pediatric drug development.

The **Office of Pediatric Therapeutics** (OPT) is **mandated** by statute to help ensure access for children to innovative, safe and effective medical products as well as coordinate and facilitate activities across FDA that may have any effect on a pediatric population, the practice of pediatrics, or involve pediatric issues.

This responsibility is particularly significant given that, historically, many medical products have not been tested for use in children. OPT provides leadership and policy direction regarding issues of pediatric health, research, and product development, and has developed a number of interrelated programs to support FDA efforts to improve the development of products for the pediatric population spanning from the neonatal period through adolescence. OPT collaborates internally with FDA centers, as well as externally with government agencies, academia, and other stakeholders to facilitate cross-cutting research projects and scientific forums to advance FDA's understanding of pediatric health and children's unique needs. In addition, OPT supports extramural research through BAAs and grants.

OPT's activities advance regulatory science through coordinating, facilitating, and conducting research projects intended to evaluate and answer important regulatory science questions relevant to informing pediatric product development, regulatory review, and safe use of pediatric products in children. OPT actively reviews and analyzes pediatric data submitted in product submissions to FDA, as well as real-world data, to identify lessons learned, develop best practices, and inform regulatory decision-making.

Oncology Regulatory Science Research

Pursuant to the 21st Century Cures Act, FDA established the Oncology Center of Excellence (OCE). It leverages the combined skills of regulatory scientists and reviewers

Oncology Regulatory Science Research

The Oncology Center of Excellence harnesses the combined skills of regulatory scientists and reviewers with expertise in the development of drugs, biological products, devices, and diagnostics to support an integrated approach to the clinical evaluation of medical products addressing cancer.

with expertise in the development of drugs, biological products, devices, and diagnostics to support an integrated approach to the clinical evaluation of medical products addressing cancer. For medical oncology products, OCE forms an interdisciplinary medical oncology review and evaluation team with representatives from the appropriate centers.

OCE oversees a robust regulatory science effort focusing on scientific research questions that arise during regulatory review of oncology products. In general, OCE emphasizes applied research that focuses on solving a specific practical problem rather than expanding general knowledge. Based on an analysis of scientific outreach activities, internal presentations, publications and technology transfer agreements, OCE identified **nine scientific priority areas and one cross-cutting area** of high interest for research. These are not the only areas of interest to OCE but represent topics with substantial existing activity.

OCE supports several intramural research projects, with a strong focus on conducting pooled analyses of clinical trial data. OCE supports extramural research projects through the BAA and CERSI programs and collaborates with some external partners using technology transfer agreements.

Rare Diseases Regulatory Science Research

The programs of the Office of Orphan Products Development (OOPD) promote and advance the development of innovative human medical products — drugs, biologics, medical devices, and medical foods — that demonstrate promise for the prevention, diagnosis, and/or treatment

of rare diseases or conditions. A rare disease is defined as any disease or condition which affects less than 200,000 persons in the US or meets the cost recovery provisions of the act. There are an estimated 7,000 rare diseases, with a public health impact that affects more than 25 million Americans and many millions more of family members in the United States. Between 85 and 90 percent of these cases are serious or life-threatening. Since the inception of the Orphan Drug Act in 1983, there have been tremendous advances in the scientific development of promising medical products. OOPD works on rare disease issues with medical and research communities, professional organizations, academia, government agencies, industry, and rare disease patient organizations and advocacy groups.

OOPD administers two grant programs that provide funding to stimulate the development of promising products for rare diseases and conditions. The Orphan Products Clinical Trials Grants Program provides funding for clinical trials that advance rare disease medical product development and evaluate safety and/or efficacy of medical products in support of a new indication or a change in labeling. The Orphan Products Natural History Grants Program provides funding for natural history studies that address knowledge gaps, remove major barriers to progress in the field, and facilitate rare disease product development.

Additionally, OOPD manages the orphan drug designation program to provide financial incentives to sponsors for developing medical products for rare diseases and conditions. OOPD evaluates requests from sponsors to determine if drugs, biologics, or medical devices meet the criteria for certain incentives (e.g., **orphan** drug, **rare pediatric disease** drug and **humanitarian use device** designations).

To facilitate efficient and successful rare disease drug development, the Center for Drug Evaluation and Research (CDER) is committed to addressing scientific and regulatory issues associated with therapeutic development in rare diseases such as the small trial populations and limited understanding of disease natural history. CDER engages in regulatory science research to address challenges in rare disease drug development to investigate flexible and feasible approaches to studying and reviewing such drugs to include: innovative use of biomarkers, consideration of non-traditional clinical development programs, use of adaptive study designs, evaluation of novel endpoints, application of new approaches to statistical analysis, and appropriate use of FDA's expedited development and review programs. CDER additionally uses mechanisms such as Broad Agency Announcements, collaborative research agreements, and memorandums of understanding to promote these efforts. The Rare Diseases Team in the Office of New Drugs, CDER is involved in many regulatory research efforts and provides training to Agency review staff related to development, review, and approval of drugs for rare diseases as part of the reviewer training core curriculum. The objective of the training is to familiarize review staff with the challenges associated with rare disease applications and strategies to address these challenges, to promote best practices for review and regulation of rare disease applications, and to encourage flexibility and scientific judgment to advance the development of rare disease therapies.

Rare Diseases Regulatory Science Research

The Office of Orphan Products Development promotes and advances the development of innovative human medical products — drugs, biologics, medical devices, and medical foods — that demonstrate promise for the prevention, diagnosis, and/or treatment of rare diseases or conditions.

One Health Initiative

The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in recognition of the inter-connectedness of human, animal, and environmental health. FDA works at the nexus of three One Health domains: (1) human health, (2) animal health, and (3) environmental health, and relies on collaboration to assist in solving complex health problems. FDA uses the One Health strategy to develop stronger cross-center and -office relationships, exchange educational experiences within the agency and with other Federal agencies, and further public and global health.

The **One Health strategy** helps FDA analyze and identify solutions to resolve health disparities in clinical trials, research, and treatments of infectious, chronic, and debilitating diseases for humans and animals. This comprehensive perspective on health and environmental problems supports inclusivity of various populations and socio-economic levels. Adopting One Health strategies also encourages FDA to take a more diverse scientific approach, which can enhance FDA's regulatory decision-making and the relevancy of policy development.

Many global changes and activities have altered interactions among people, animals, and the environment. For example, using the One Health approach:

- FDA studies factors that give rise to zoonotic transmission (diseases that can spread from animals to people) when there are disruptions to human and animal interactions caused by changes in ecology, thus affecting public health challenges and concerns (e.g., avian influenza, Ebola virus disease, tick-borne diseases, West Nile virus, Zika virus, and coronavirus).

- FDA conducts studies to look at ecological relationships on farms to reduce foodborne contamination and illnesses and protect the global food supply. Here, FDA surveilles the geographic variation of foodborne pathogens in water for agricultural use to better understand the environment's relationship to foodborne contamination and public health.

- FDA submits foodborne pathogen genomes identified in their foodborne outbreak studies to the **National Center for Biotechnology Information Pathogen Detection web portal** for surveillance and source tracking of pathogens. By sharing whole genome sequencing (WGS) data in a public and global database, all stakeholders can quickly see whether there is a One Health connection to their pathogens.

In addition, a central theme of the **National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) 2021-2025 Strategic Plan** is One Health. FDA is an active member in NARMS, a multi-agency public health surveillance system conducting surveillance of antimicrobial use and WGS resistance data to better track resistance trends and outbreaks in foodborne and other enteric (intestinal) bacteria. In accordance with the principles of One Health, NARMS is expanding its testing to include environmental water samples through a collaboration with the U.S. Environmental Protection Agency and animal pathogens through collaborations with FDA's Veterinary Laboratory Investigation and Response Network and U.S. Department of Agriculture Animal and Plant Health Inspection Service. **Learn more about the One Health Initiative at FDA**.

FDA One Health Mission

FDA collaborates with stakeholders across disciplines and sectors to promote the health of humans, animals, and the environment using science, technology, and innovation.

FDA One Health Vision

Optimal public health outcomes for humans and animals in their shared environment.

FDA Strategic Initiative	Focus Area of Regulatory Science	Regulated Product Lifecycle			
		Product Characterization, Manufacturing, and Quality	Non-Clinical Pre-market Evaluation	Clinical Pre-market Evaluation	Post-market Activities
Public Health Preparedness and Response	Medical Countermeasures and Preparedness for Emerging Infectious Diseases	✓	✓	✓	✓
	Technologies to Reduce Pathogen Contamination	✓	✓	✓	✓
	Substance Use Disorders	✓	✓	✓	✓
	Antimicrobial Resistance	✓	✓	✓	✓
	Food Safety	✓	✓		✓
	Quality of Compounded Drugs				✓
Increasing Choice and Competition through Innovation	Individualized Therapies and Precision Medicine	✓	✓	✓	✓
	Complex Innovative Trial Design			✓	
	Microbiome Research	✓	✓	✓	✓
	Novel Foods and Food Ingredients	✓	✓	✓	✓
	Regenerative Medicine	✓	✓	✓	✓
	Advanced Manufacturing	✓			✓
	Increasing Access to Complex Generic Drug Products	✓	✓	✓	✓
	Biomarkers	✓	✓	✓	✓
	Novel Technologies to Improve Predictivity of Non-Clinical Studies and Replace, Reduce, and Refine Reliance on Animal Testing	✓	✓		
	Model-Informed Product Development	✓	✓	✓	
Unleashing the Power of Data	Product Safety Surveillance				✓
	Artificial Intelligence	✓	✓	✓	✓
	Digital Health	✓	✓	✓	✓
	Use of Real-World Evidence to Support Medical Product Development and Regulatory Decision-Making			✓	✓
Empowering Patients and Consumers	Patient and Consumer Preferences and Perspectives	✓	✓	✓	✓
	Patient-Reported Outcomes and other Clinical Outcome Assessments			✓	✓
	Empowering Patients and Consumers to Make Better-Informed Decisions				✓

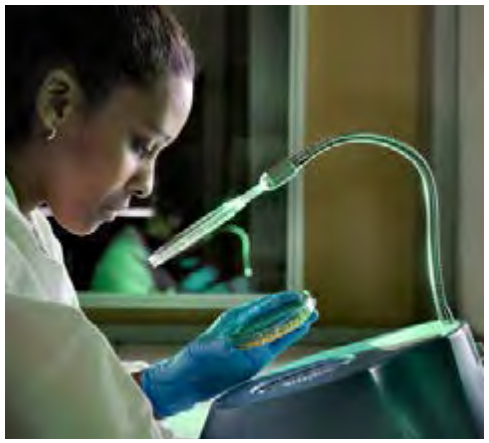
Lifecycle of FDA-Regulated Products

As part of its regulatory responsibilities, FDA regulates products at different stages of the lifecycle, depending on the type of product. Regulatory science research is conducted across the phases of the product lifecycle to facilitate product assessment and evaluation, help make better-informed regulatory decisions, and increase the quality, consistency, and safety, or to reduce the associated harms, of FDA-regulated products. For example, if FDA researchers develop an improved understanding of the mechanisms of action of a complex biologic, then this information could augment guidance that FDA provides to product developers on issues such as how to choose critical quality attributes for product characterization, potency assays, and assessment of quality.

FDA researchers also engage in development and evaluation of new methods and models to identify approaches with improved predictive value or that may **replace, reduce, and refine (the 3 Rs) the use of animals in research**. Current paradigms of clinical evaluation generally result in sometimes costly and time-consuming clinical trials to generate sufficient data to support licensure, approval, or clearance of an FDA-regulated medical product. Therefore, a combina-tion of improved non-clinical evaluation and new ways to perform clinical evaluation may help reduce cost, time, and the risk of developing new and innovative products. Finally, FDA is committed to advancing and protecting the public health through its oversight of FDA-regu-lated products. To fulfill this commitment, FDA aims to improve the data sources and analytical approaches to support post-market activities. View how the FARS apply to the product lifecycle in the table on page 16.

FOCUS AREAS OF REGULATORY SCIENCE

Public Health Preparedness and Response



Introduction

FDA prepares to respond to a wide variety of natural and human-caused threats and public health emergencies (e.g., COVID-19) that involve, affect, or require the use of FDA-regulated products to help keep the public safe. FDA carries out many activities to protect and advance public health and to prevent and respond to public health emergencies.

In response to a public health emergency, FDA's research amplifies the many regulatory activities that take place. This includes development of standards, panels, and reagents to help speed the development and availability of potential vaccines, diagnostics and therapeutics; maintaining and securing drug supply chains; expediting approval of generics to help alleviate drug shortages; providing guidance to food and medical device manufacturers; advising developers on clinical trial issues; and keeping the public informed with fact-based health information. FDA oversees the repurposing of existing drugs and the development and approval of new drugs and vaccines by working with potential manufacturers and sponsors to rapidly move products into clinical trials, while helping to ensure the trials are properly and safely designed.

FDA actively communicates in real-time with hospitals across the United States and external stakeholders about their drug supply needs. FDA builds capacity through partnerships, including the **Laboratory Flexible Funding Model** to increase chemical, radiological and microbiological resources for domestic partners to respond to public health events.

Medical Countermeasures and Preparedness for Emerging Infectious Diseases

Importance to FDA

Medical countermeasures, or MCMs, are FDA-regulated products (biological products, drugs, devices) that may be used to diagnose, prevent, mitigate, or treat conditions associated with a potential public health emergency stemming from a terrorist attack with a chemical, biological, radiological, or nuclear (CBRN) material, or a naturally occurring emerging disease (e.g., COVID-19 and pandemic influenza). FDA is responsible for reviewing the safety, effectiveness, and quality of MCMs and contributes its regulatory science expertise to address priorities of the **Public Health Emergency Medical Countermeasures Enterprise**, a coordinated cross-U.S. government effort working to enhance CBRN preparedness including those against emerging infectious diseases. FDA also works closely with the U.S. Department of Defense (DoD) to facilitate the development and availability of MCMs to support the unique needs of American military personnel, including a framework established in fiscal year 2018 under **Public Law 115-92 for enhanced FDA/DoD collaborations**. In 2010, FDA launched its **Medical Countermeasures Initiative Program**, building on the substantive MCM work ongoing at FDA and focusing increased resources on promoting the development of MCMs by establishing clear regulatory pathways for MCMs, instituting effective regulatory policies and mechanisms to facilitate timely access to available MCMs, and advancing MCM regulatory science to create the tools that support timely regulatory decision-making.

Developing MCMs often presents unique challenges. For example, commercial markets generally lack the incentive to develop MCMs. Further, limited exposure to threat agents, such as anthrax, often makes it difficult to generate the necessary data from traditional clinical trials to support regulatory review and decision-making. In some cases, clinical trials may not be feasible or are unethical. In these cases, it may be necessary to use data from adequate and well-controlled animal efficacy studies under regulations commonly known as the **Animal Rule** (applicable only to certain products regulated by the Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research). Additional challenges

include ethical considerations for participation in clinical trials for special populations (e.g., pregnant women and children). FDA researchers respond to these challenges by applying innovative science and developing standards, tools, and strategic approaches to support safe and effective MCMs.

Examples

- Developing **reference materials** to facilitate evaluation of specific and sensitive diagnostic devices for emergent viruses (e.g., SARS-CoV-2 and Zika virus).
- Conducting studies to apply systems biology and machine learning approaches to strengthen models of coronavirus disease.
- **Characterizing coronavirus** (SARS-CoV-2/variants, SARS-CoV, and MERS-CoV,) host-pathogen responses to identify biomarkers of disease progression and severity.
- Developing novel analytical tools for quality control for next-generation sequencing databases (e.g., FDA ARGOS).
- Describing pathogenicity and immunity to **Ebola and SARS-CoV-2 in nonclinical and clinical studies**.
- Explaining host factors contributing to immune responses to Zika, **Ebola**, and **SARS-CoV-2** to more rapidly predict patient outcomes and addressing health care needs of diverse patient populations.
- **Characterize the natural immunity** in Ebola Virus Disease (EVD) and Marburg Virus Disease (MVD) survivors as well as the durability and correlates of vaccine-induced immunity to EVD
- Developing and evaluating a variety of **microphysiological systems** to use as tools to support development of MCMs for **acute radiation syndrome** (radiation sickness) and **COVID-19**.
- Developing methods to detect African swine fever virus in animal food and food components.
- Developed and validated two methods to detect and quantify alcohols and impurities in gel and liquid hand sanitizers during the COVID-19 pandemic. The methods, which are capable of simultaneously identifying multiple alcohols, represent a significant improvement over the existing technology, and were applied to hundreds of hand sanitizer samples that were suspected to be adulterated with unacceptable alcohols, such as methanol. The laboratory findings resulted in recalls, warning letters, import alerts, and placement of products on FDA's list of hand sanitizers that consumers should not use. This research provided a substantial improvement both in throughput and multi-analyte detection, consistent with the needs of a national emergency scenario.
- Conducting research to characterize patients with cancer after recovery from COVID-19, and investigating COVID-19 sequelae, vaccination, breakthrough infections, and the potential impact of COVID infection on treatment and safety of approved medical products.
- Qualified an animal model to demonstrate the efficacy of therapeutics for treatment or post-exposure prophylaxis of pneumonic tularemia. This was the first animal model qualified under the FDA Animal Model Qualification Program.
- Expanding the CURE ID platform (developed by FDA and NCATS) to allow automated data collection from electronic health records (EHR) worldwide and clinical disease registries for COVID-19 and other difficult-to-treat infectious diseases. The Critical Path Institute is convening a public-private partnership (CURE Drug Repurposing Collaboratory). Health care providers and researchers interested in patient-centered outcomes research for COVID-19 and other infectious diseases would have access to comprehensive (de-identified) case reports on potentially tens of thousands of patients, including treatment outcomes, such as recovery, deterioration, hospitalization, ICU admission, and death.
- Completed studies to develop methods for respirator decontamination and reuse in emergencies, which resulted in the **first consensus standard for UV surface decontamination** and provided **data to support EUA of the CCDS Critical Decontamination System** used to reduce N95 shortages during the COVID-19 public health emergency.

- Leveraged the **Sentinel System** to **inform study protocols** to evaluate safety and effectiveness of MCMs for influenza and COVID-19, and provide a baseline for comparison during a public health emergency.
- Completed studies that **enhanced understanding of Ebola and COVID-19 host-pathogen** responses to support MCM development.
- Completed studies **characterizing immune responses** to Ebola and SARS-COV-2 in vaccinated and infected individuals inform vaccine development and review.
- Completed high-quality sequencing of over 1000 bacterial, viral, and fungal organisms to be added to the FDA **ARGOS** database.

Technologies to Reduce Pathogen Contamination

Importance to FDA

A major public health safety concern is the risk of transmissible infectious diseases associated with the use of FDA-regulated medical products, consumption of food, or reuse or sharing of medical devices. In the medical product space, this is a challenge because many medical products cannot be terminally sterilized (meaning they're sterilized in their final holding container) since some are composed of biological materials that may lose their ability to work as intended. Examples of biological materials include human blood and blood components, therapeutic proteins, monoclonal antibodies, live virus vaccines, certain gene therapy products, and cell-based therapies.

To address these issues, FDA encourages the development of tools designed to evaluate innovative technologies to reduce, inactivate, or eliminate pathogens from FDA-regulated products. The Agency combines typically used methods in conjunction with novel tool development to prevent transmission of infectious disease through FDA-regulated product use. Typical and novel methods incorporate one or more of the following:

- Prevention (e.g., using carefully sourced raw materials); or
- Reduction, inactivation, or elimination, e.g., irradiating devices and certain foods, terminally sterilizing drugs, removing, or inactivating methods applied to traditional biotechnology products or to certain foods; or
- Detection, e.g., screening of the blood supply to remove units carrying human pathogens, sampling and testing foods and removing those containing foodborne pathogens from the marketplace.

Examples

- FDA has regulatory oversight for the safety of human blood and tissues. The risk of transfusion-transmitted diseases in blood products has decreased significantly, and there continues to be low rates of transfusion-transmitted infectious diseases associated with the blood supply due to the development of specific assays for detection of known human pathogens and donor deferral policies. FDA evaluates and encourages development of simple and innovative technologies for effective pathogen reduction of whole blood and red blood cells and encourages improvement of existing technologies developed for platelets and plasma to continue improving the safety of the blood supply.
- Investigating whether the application of nanopore technology makes it easier to detect and trace the Clostridium botulinum (C. botulinum) toxin and Escherichia coli (E. coli). New immune-based methods are being developed to enable rapid and sensitive detection of toxins in food substrates, such as C. botulinum, ricin, and abrin.
- FDA has regulatory oversight for the safety of foods other than meat, poultry and processed egg products. FDA conducts research on the use of technologies such as high--pressure processing, non-thermal plasma, and thermal inactivation of pathogens in various food matrices. FDA also conducts research on new detection methods and the application of whole genome sequencing of microbial pathogens to identify outbreaks of illness and new sources of contamination and encourages industry to adopt new

measures to control foodborne pathogens.

- FDA has been working with industry to identify microbial contamination in tattoo inks and address ways to eliminate this problem. Some of these activities have included regulatory meetings to address issues of sterility and manufacturing processes, as well as working to identify the different types and quantity of microbes present in the inks using BAM chapter 23, USP 71 and are beginning to look at other methods to reduce time for testing.

Substance Use Disorders

Importance to FDA

Substance use disorders are the persistent use of substances with abuse potential such as opioids, stimulants, cannabis, or nicotine-containing tobacco products, despite substantial harm and adverse consequences. Substance use disorder and fatal overdoses may usually involve multiple substances, often from different drug classes. In the United States, opioid use-related death is a recognized public health emergency.

In addressing the opioid crisis, the **Agency priorities include**:

1. Decreasing Exposure and Preventing New Addiction
2. Supporting Treatment of Those with Opioid Use Disorder
3. Fostering Development of Novel Pain Treatment Therapies
4. Improving Enforcement and Assessing Benefit-Risk

While there are several FDA-approved medications for treatment of opioid use disorders (**containing buprenorphine, methadone, or naltrexone as active ingredients**), there are no therapies for certain vulnerable populations such as: (1) young adolescents; and (2) neonates exposed to opioids in utero and who suffer withdrawal upon birth. Additionally, there are currently no FDA-approved medications for treating stimulant use disorders, which is why the Agency is focusing on supporting development of such treatments, as well as treatments for cannabis use disorder, alcohol use disorder, substance withdrawal syndromes, and a variety of other substance use disorders.

FDA is also concerned with the negative health effects associated with tobacco product use. The Agency reviews, among other things, the toxicity and potential abuse liability of new tobacco products before they can be introduced into interstate commerce.

Examples

FDA supports or performs research to address substance use disorders and adverse consequences of drug use:

- Developing a national-level system dynamics model of the opioid crisis to inform assessment of new opioid policy initiatives. The model provides a tool for assessing patterns, contributing factors, and trajectories of problematic prescription and illegal opioid use and substance use disorders.
- Conducting targeted nonclinical and clinical studies to evaluate respiratory risk associated with the simultaneous use of opioids and other sedative psychotropic drugs and developing mechanistic-based computational models to predict required naloxone dosing for reversal of opioid overdose.
- Evaluating infants receiving opioid replacement drug therapy for opioid withdrawal syndrome for potential impairment of the growth and development of the brain and/or central nervous system.
- Creating and participating in partnerships with other Federal agencies and external organizations to build data infrastructure, refine study methodologies, create data linkages, and improve the quality of data that can be used to evaluate substance abuse trends and related adverse outcomes.
- Supporting extramural research projects to better understand the trajectories of substance use and use disorders, with particular focus on the development of stimulant use disorders and the relationships between prescription and illicit stimulant use.

- Supporting collaborative research focused on the abuse liability of tobacco products, including examinations of nicotine pharmacokinetics, product use behaviors, and subjective effects to better understand the addiction potential of many different tobacco products.

- In May 2018, FDA launched an opioid crisis innovation challenge to help combat the opioid crisis and achieve the goal of preventing and treating opioid use disorder. The initiative is intended to spur the development of medical devices, including diagnostic tests and **digital health** technologies.

Antimicrobial Resistance

Importance to FDA

Antimicrobial resistance (AMR) refers to a change in a microorganism that makes it resistant to antimicrobial products (e.g., antibacterial, antiviral, or antifungal drugs). Antimicrobial products used to treat infections lose effectiveness when microorganisms become resistant. AMR remains a significant global public health threat: according to the Centers for Disease Control and Prevention (CDC), each year in the United States, at least 2.8 million antibiotic-resistant (a subset of AMR) infections occur, and **more than 35,000 people die as a result**.

FDA participates in and contributes to the Combating Antibiotic-Resistant Bacteria (CARB) Task Force, a U.S. government-wide, interagency effort tasked with addressing AMR challenges. This group implements priorities outlined in the **Presidential Advisory Council on CARB National Action Plan**. In addition, the FDA Antimicrobial Resistance Taskforce and related workgroups collaborate with other government agencies and external stakeholders to develop approaches to detect, prevent, and limit the impact of AMR. FDA facilitates development of enhanced diagnostic and surveillance tools and develops standards to detect AMR early, monitor it, and minimize resistance development. FDA also works to improve these approaches to better understand how AMR occurs and spreads. In addition, FDA facilitates development of new drug and biological products to prevent or treat infections, including new antimicrobial products (e.g., bacteriophage therapy—the use of viruses that invade and kill bacterial cells).

Examples

- The **CDC and FDA Antibiotic Resistance Isolate Bank** is a resource of diverse antibiotic resistant strains of bacterial isolates that manufacturers can use to validate diagnostic assays to detect antibiotic resistance. Availability of isolate panels supports innovation in diagnostics and drug development. FDA uses data from product developers generated with the panels to evaluate drugs and medical devices, such as those with infection-preventing technologies.

- FDA takes a One Health approach to monitoring for AMR in bacteria—a strategy that leverages the interconnection between people, animals, plants, and their shared environment. As a NARMS partner with CDC and the US Department of Agriculture (USDA), FDA monitors bacteria sampled from retail meats and seafood for AMR and engages in research to explore expanded testing.

- FDA's Veterinary Laboratory Investigation and Response Network (Vet-LIRN) plays an important role in One Health monitoring for AMR in veterinary pathogens collected from companion animals.

- FDA leads the **Systemic Harmonization and Interoperability Enhancement for Lab Data (SHIELD)** initiative, which aims to improve the accessibility, shareability, and quality of laboratory data supporting evaluation of in vitro diagnostics.

The SHIELD initiative helps laboratories across its multi-agency and stakeholder network (e.g., National Institutes of Health, non-governmental organizations such as Pew Charitable Trusts, academia) to better understand clinical management practices and health outcomes, specially to address antimicrobial resistance due to timely discovery of patterns in interoperable data repositories.

- Scientific approaches are applied to develop targeted patient therapies and more rapid control measures to reduce infection development. Examples include advancing the science of clinical trial design, evaluating novel strategies such as combination antimicrobials, and studies of non-traditional antimicrobial products, such as bacteriophage therapy, understanding mechanisms of resistance to minimize its evolution, and facilitating development of diagnostic devices to detect infection by AMR organisms earlier.

- FDA researchers are developing tools to efficiently assess the role of plasmids (genetic structures outside of the bacterial chromosome that often carry genes encoding AMR and/or virulence traits) that can be spread among pathogens. These efforts are targeting understanding factors that increase the ability of resistance plasmids to be transmitted among bacteria spreading AMR.

- FDA performs studies and develops models to facilitate the development of safe and effective vaccines against pathogens such as *Mycobacterium tuberculosis, Neisseria gonorrhoeae,* and *Clostridioides difficile*. Effective preventive vaccines indirectly decrease the need for antimicrobial use. Thus, availability of vaccines preventing infection of these and **other pathogens with high rates of AMR** may prolong the usefulness of antimicrobial agents and reduce the development of multi-drug resistant pathogens.

- FDA explores strategies to prevent the emergence of bacterial resistance. Using a hollow fiber system, FDA has demonstrated that combinations of three antimicrobials may prevent the emergence of high-level resistance that occurs during treatment with a single antibiotic. Ongoing animal studies are determining whether combination therapy has a harmful impact on the microbiome. This work might help to inform further development of clinical approaches to reducing emergent bacterial resistance.

Food Safety

Importance to FDA

FDA faces unique challenges in the oversight of human and animal food safety. The source of these challenges involves factors that are driven, in part, by globalization, the increasing complexity of international supply chains of human and animal food and changing consumer demands. FDA oversees **about 78 percent** of the U.S. food supply, covering all foods (including dietary supplements), except for meat, poultry, catfish, and some egg products. This oversight involves continuous surveillance of the human and animal food supply for ongoing and emerging threats, development of methods for detecting and countering threats, and deployment of those methods to domestic and global partners. FDA prioritizes communicating results and activities related to food supply to ensure the safety of the public and their animals.

Examples

Below are some of the ways that FDA regulatory science research supports food safety:

- Using WGS to investigate pathogen (bacteria, viruses and the parasite cyclospora cayetenensis) contamination of human foods and contamination of animal food that may have been potentially exposed and shared with humans. WGS is used to: (1) characterize selected pathogens; (2) provide linkages between food or environmental samples to human clinical illnesses, that might not be found with routine testing; and (3) provide the foundation for metagenomic methods as they are increasingly applied to identifying pathogens.

- Evaluating dietary exposure to per- and polyfluoroalkyl substances (PFAS), as a result of environmental contamination of food. PFAS are human-made chemicals used in a variety of applications

including in stain- and water-resistant fabrics and carpeting, cleaning products, paints, and fire-fighting foams. FDA researchers are at the forefront of developing new comprehensive and more sensitive testing methods to measure low levels of PFAS concentrations in food. The validated analytical methods have has been used to test a wide variety of foods in FDA's Total Diet Study, targeted sampling of certain commodities such as seafood, as well as FDA- regulated products that are grown in areas with environmental PFAS contamination.

- Investigating relationships between increased reports of dilated cardiomyopathy in dogs and the consumption of certain dog foods containing high amounts of ingredients such as peas, chickpeas, lentils, and specific types of potatoes.

- Developing and validating methods to detect food contaminants and unapproved product irradiation in diagnostic samples from animals that consume pet food, and pet treat products, and pet treats. Testing diagnostic specimens provides insights into consumer complaint case investigations. Such investigations require validated methods for diagnostic samples from animals such as urine, blood, feces, saliva, liver, and kidney.

- Enabling the expansion and validation of detection methods via multi-laboratory projects through the **Veterinary Laboratory Investigation and Response Network (Vet-LIRN)** program enables the expansion and validation of detection methods via multi-laboratory projects, thereby increasing the number of validated methods available to Vet-LIRN labs during outbreaks or other emergency events. The program also strengthens collaborations between network laboratories, which is crucial for providing a quick response in an emergency.

- Substantially increasing sample throughput to improve detection of disallowed veterinary drug residues in honey intended for human consumption. We have done this by modifying the existing method of analysis, providing additional data and tools to the agency to inform regulatory analysis and policy.

- Implementing a laboratory flexible funding model (LFFM) which offers funding to states to engage in different projects that have been prioritized by the agency. LFFM serves to leverage state capacity for high-priority agency projects, stimulates methodology and technology transfer with state partners, and provides FDA with an expanded network of

labs that can collaborate to provide vigilance and monitoring on FDA regulated products.

- Evaluating and approving the data and methods submitted by manufacturers who market rapid-screening tests for detecting antibiotic drugs in Grade A raw milk. Such rapid screening is imperative to ensure safety of the US milk supply because this perishable commodity needs to be tested on the spot.

- Developing and validating a high-resolution mass spectrometric method for the quantitation and confirmation of multiple veterinary drug residues in raw milk. This supports regulatory decision-making on veterinary drug residues in raw milk to help keep the nation's milk supply safe for human consumption.

- Developing and validating xMAP® food allergen detection assay (xMAP FADA) to overcome the limitation of the commonly used ELISA as a regulatory method for allergen detection. It is a multi-plex immunoassay that allows detection of many different food allergens simultaneously, currently 14 allergens plus gluten, and continues to be expanded to more allergens, such as sesame.

- Developing chemical methods such as rapid screening for honey for adulterants, detection of foreign oils in olive oil, and authentication of extra virgin olive oil. Economically motivated adulteration (EMA) is not just an economic issue as food fraud but can lead to health issues and even death, such as in the case of melamine (2008). To fight the everchanging ways fraud is committed, FDA researchers must be creative and proactive in developing methods to detect possible adulterations.

- Developing DNA barcoding to ensure consumers receive the fish they purchased.

Quality of Compounded Drugs

Importance to FDA

Compounding is generally a practice in which a licensed pharmacist, a licensed healthcare professional, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient. Although compounded drugs can serve an important medical need for certain patients, they also present special risks. Compounded drugs are not reviewed by FDA for safety, efficacy, or manufacturing quality before they are marketed.

In 2012, contaminated drugs compounded by a Massachusetts pharmacy led to more than 750 cases of serious infections and over 60 deaths in 20 states, resulting in the enactment of the **Drug Quality and Security Act (DQSA, Public Law 113-54)**. The DQSA established a new category of compounders (outsourcing facilities), which are held to more stringent quality standards and are inspected by FDA according to a risk-based schedule. FDA's compounding program aims to protect patients from unsafe, ineffective, and poor-quality compounded drugs, while preserving access to lawfully marketed compounded drugs for patients who have a medical need for them. FDA is engaged in efforts aimed to reduce risks related to compounded drugs, including research on bulk drug substances used in compounding and research, training, and educational initiatives through FDA's **Compounding Quality Center of Excellence**.

Examples

- FDA engages in significant research and analysis on bulk drug substances (active pharmaceutical ingredients) that may be used in compounding under federal law. These ongoing initiatives involve dedicated efforts of numerous clinicians, scientists,

and researchers to understand available information on clinical use, safety, and effectiveness for bulk drug substances used in compounded drugs. FDA also engaged with the following external research partners to inform these efforts and agency decision-making generally, as well as inform the public:

- The National Academies of Science, Engineering & Medicine (NASEM) conducted **research on the safety and effectiveness of multi-ingredient compounded topical pain creams** and concluded, among other things, that there is limited evidence to support the use of compounded topical pain creams in the general adult population.

- NASEM also conducted research to **assess treating patients with compounded hormone therapy (HT) products and the availability of scientific evidence for their safety and efficacy**. NASEM's report found that there was a lack of rigorous evidence of safety and effectiveness from well-designed or properly controlled clinical studies.

- The University of Maryland CERSI engaged in two research efforts: a **three-year effort to examine the clinical use of drugs compounded from certain bulk drug substances**, engaged in a three-year effort to examine the clinical use of drugs compounded from certain bulk drug substances and a two-year effort to obtain additional information about certain bulk drug substances.

- The **Johns Hopkins University CERSI** conducted **research to evaluate available evidence on the safety and effectiveness of each of six bulk drug substances** used in compounded drugs for patients with autism spectrum disorder.

- FDA has advanced the Compounding Quality Center of Excellence to improve the quality of compounded drugs. This major initiative includes education, outreach, and research initiatives, including regulatory science projects involving multiple FDA labs:

  - FDA initiated a Landscape Study of the outsourcing facility sector to better understand barriers and opportunities encountered by outsourcing facilities in three major areas: compliance with current good manufacturing practice (CGMP)/good quality drug production, market and business viability, and interactions with FDA. The research provides insights that FDA can use to identify future FDA training topics, understand the effects of FDA policy on the sector, inform areas that FDA can increase engagement with outsourcing facilities, and enhance Compounding Quality Center of Excellence program areas.

  - As part of the Compounding Quality Center of Excellence's focus on regulatory science, FDA has projects underway related to compounding operations, including a study that evaluates commercially obtained sporicidal disinfectants to strengthen the scientific framework by building an accurate efficacy database of these products, which will provide additional information regarding their use by compounders.

Increasing Choice and Competition through Innovation

Introduction

Scientific and technological innovation addressing public health needs are important drivers for FDA's regulatory portfolio. To support the development of innovative products, FDA's regulatory science research addresses knowledge gaps and improves the Agency's familiarity with how new science and technology are applied to FDA-regulated products. FDA's **Emerging Sciences Working Group** scans the horizon to identify new scientific trends that may affect products coming to FDA in the future. The identification of trends in this horizon-scanning may result in a new scientific working group, new employee recruitment, funding of intramural and extramural projects to address FDA's needs, and new training programs or provision of other resources to FDA reviewers. FDA adapts and responds by actively promoting scientific and technological innovations, using innovative research tools to further advance development of innovative regulated products, and providing support and information about regulatory requirements to other innovators.

Individualized Therapeutics and Precision Medicine

Importance to FDA

Most medical treatments are designed for the average patient, which may be successful for most but not all patients. Individualized therapeutics are products to designed to treat one to a few individuals to address unmet health needs. Individualized therapies have become increasingly feasible due to improved understanding of individual variability and identifying new rare genetic diseases with next generation sequencing (NGS) technologies. The challenges and opportunities for utilizing FDA-regulated products as individualized therapeutics span the product lifecycle: the development of robust manufacturing and assurance of product quality, extent of preclinical testing to support regulatory evaluation, and the collection of clinical evidence with a very small number of patients worldwide (e.g., populations as small as one patient). These issues impact safety and effectiveness evaluation and sustainability.

Precision medicine—sometimes known as personalized medicine—tailors disease prevention and treatment for individual variability (e.g., genetic and lifestyle differences among patients). The goal of precision medicine is to match the right treatments at the right dosages for each individual patient at the right time. The challenge for precision medicine is identifying the mechanistic basis for adverse events, such as why the body reacts negatively to a treatment (e.g., breaking out in a rash) and differences in efficacy (e.g., why a drug works better in some patients than it does in others).

To realize the promise of precision medicine and individualized therapeutics, FDA sees a critical need for more mechanistic understanding, improved manufacturing capabilities, and additional tools. FDA is exploring new technologies (e.g., *omics*) to advance major breakthroughs in diagnosis, prognosis, and treatment of diseases. FDA created **precisionFDA**, a cloud-based portal for community research and development that allows users world-wide to share data and tools to test, pilot, and validate existing and new bioinformatics approaches to NGS processing.

For example, pharmacogenetics studies how individuals respond differently to drug therapies based on their genetic make-up using technology such as NGS which allows sequencing of a human's entire genome in a short period of time (as short as one day). This technology combined with others enables researchers to identify precise genetic, mechanistic, or lifestyle reasons to understand why certain individuals or subpopulations respond positively or negatively when treated for the same disease with the same drug. Being able to more precisely classify the genetic basis of diseases and drug responses through

diagnostic tests and devices enables development of mechanistically targeted therapeutics.

Examples

- Bacteriophage (phage) therapy (i.e., the use of viruses that invade and kill bacterial cells) is being investigated as a novel antimicrobial approach to treat antibiotic resistant bacterial infections. To overcome bacterial resistance of conventional antibiotic treatment, personalized bacteriophage cocktails are used as treatment for the patient's unique bacterial strain. FDA is developing and evaluating animal models to assess safety and effectiveness of bacteriophage cocktails for treating antibiotic resistant bacterial infections.

- **Gene therapies**, such as adeno-associated virus (AAV) vectors and CAR T cells show promise for treating several types of rare genetic and intractable diseases, with some products already approved, and ex vivo modified cells, often using lentiviral vectors for gene delivery, have been found to be effective at treating disorders of the hematopoietic system. In addition, genome editing tools that can directly repair genetic defects, are being explored to allow rapid development of individualized therapies. However, there are still challenges that need to be addressed before these complex therapeutic strategies can be deployed for more routine use. This includes predicting or avoiding immunogenicity of the vector (e.g., AAV) or therapeutic gene, creating more efficient and scalable manufacturing methods, and developing more reliable ways to identify and understand the potential for unintended changes to the genome that may have negative consequences.

- Pharmacogenetic tests are of increasing interest to healthcare practitioners in selecting therapeutic agents and avoiding harmful treatments. FDA published a **Table of Pharmacogenetic Associations** to increase the quality of scientific evidence supporting clinically available tests. This resource provides transparency into FDA's view of the state of scientific evidence in pharmacogenetic gene-drug associations, and where the evidence is enough to support therapeutic management recommendations for patients with certain genetic variants, or genetic variant-inferred phenotypes that are likely to have altered drug metabolism, and in certain cases, differential therapeutic effects. This is an important step toward supporting well-qualified therapeutic decisions by medical professionals.

- FDA researchers answer critical regulatory science questions related to drug approval in use of immunotherapy, as well as other new drugs for acute myeloid leukemia (i.e., a cancer of the blood and bone marrow), lung cancer, and other malignant conditions. This includes understanding the genetics of immune-related harmful events and investigating genetic signatures (i.e., information about a group of genes) associated with the impact of drug toxicity or efficacy.

Complex Innovative Trial Design

Importance to FDA

In response to the quickly changing drug development landscape, FDA is concentrating efforts to advance Complex Innovative Trial Designs (CIDs). CIDs include complex adaptive, Bayesian, and other novel clinical trial designs. CID has design elements and/or analysis approaches that generally require computer simulations to determine the statistical properties of the trial (e.g., power, Type I error). FDA administers a **CID Pilot Meeting Program** (CID Program) to support the goal of facilitating and advancing the use of CIDs. The CID Program offers sponsors, whose meeting requests are granted, the opportunity for increased interaction with FDA staff to discuss their proposed CID approach, and fulfills a performance goal agreed to under the **Prescription Drug User Fee Amendments (PDUFA VI)**, which was enacted as part of **FDA Reauthorization Act of 2017 (Public Law 115-52)**.

A goal of this program is to work with sponsors to maximize clinical trial efficiency while using scientifically sound methods to determine the design for the question and population of interest. FDA's goal is to extend using CIDs, where appropriate, from exploratory studies to clinical trials intended to provide substantial evidence of effectiveness to support regulatory approval of new therapies. A common feature of many CIDs is the need for

simulations to estimate a variety of trial parameters. CIDs do not change FDA's expectations that clinical trials be sufficient to evaluate safety and effectiveness of drug use in the intended population including pertinent subsets, such as gender, age, and racial subsets. Advancing the use of CIDs requires further research as described in the examples below.

Examples
FDA applies multiple strategies to address the regulatory science needed to facilitate implementing CIDs:

- Evaluating the use of master protocols, which may include umbrella, basket, or platform trials. These trials allow for the evaluation of multiple therapies in a single disease, a single therapy in multiple diseases, or multiple therapies in a single disease, with therapies entering or leaving the trial based on a decision algorithm, respectively.

- Using Sequential Multiple Assignment Randomized Trials to provide a statistical framework for evaluating potentially complex treatment algorithms.

- Evaluating Bayesian approaches for the potential to increase clinical trial efficiency. For example, Bayesian trial designs may incorporate data external to the trial in a formal mathematical framework to maximize the use of information sources.

- Exploring new approaches for statistical analyses of oncology trials, where the COVID-19 pandemic has affected participation/enrollment and the estimate specified in the original trial design.

Microbiome Research

Importance to FDA
FDA regulates many products and devices that interact directly or indirectly with the human and animal microbiomes. Microbiota refers to the community of microbial species connected by physical location, inter-relationships of function, and microbiome to the collective genomes. For example, the human body's microbiome is made up of trillions of beneficial, neutral, and pathogenic microbes.

FDA's microbiome research spans microbiology, toxicology, nutrition, immunology, and antimicrobial resistance because animal and environmental microbiota play important roles in states of health and disease. Diet, antibiotics, drug and chemical residues in food, cosmetics, and metabolites of all of these factors may influence complex processes regulated by the microbiome that are important to human health. FDA regulates some products that are composed of or impact microbes and/or microbial communities, such as fecal microbiota for transplantation (FMT), live biotherapeutic products, live microbes in foods, dietary supplements, and tobacco products.

Examples
FDA researchers address key issues related to FDA-regulated products and their impact on the microbiota, often through studies of the microbiome.

- Developing and using an animal model to assess FMT: Using infection by the gastrointestinal pathogen *Clostridioides difficile (C. diff.)* as a model, researchers are assessing safety methods, seeking to understand how manufacturing procedures alter microbial composition, and are working to identify biomarkers of an effective microbial community to assess the potency of FMT products. This work uses next generation sequencing methods and an animal (murine) model with a unique microbiome that is naturally resistant to *C. diff*.

- Addressing the impact of FDA-regulated medical products on gut microbiota and natural immune response to highlight the different physical reactions to gut microbiota. Uncovering the gut microbiota response to a drug or biological product may help identify individuals in the population more likely to positively respond to therapy. Thus, these gut microbiota responses may inform recommendations to facilitate development of biologics and small molecule drugs.

- FDA scientists are optimizing an intestine-on-a-chip model for measuring the impact of drug residues on the human intestinal microbiome – for use as a potential alternative in vitro model to support

evaluation of new animal drug products. Developing a qualified model that can serve as a potential alternative to animal testing represents a substantial step forward in the evaluation of new animal drug products and aligns with FDA's efforts to reduce or refine reliance on animals for research.

- Many products available to the consumer, such as dietary supplements and foods, contain intentionally added live microorganisms that may provide a human health benefit. This has led to an increased production of these commodities to meet the demand for these new health related supplements. Consumers rely on product labels that report identity and viability to be accurate and true. However, species are often misclassified, or absent, and products are occasionally contaminated with species not listed on the label. High-throughput next generation sequencing (NGS) can support metagenomic investigations as a feasible means to analyze these products and eliminate any bias of culture-based sampling, or the inability to isolate all microbes present.

- Studying the degree to which tobacco use is associated with negative effects on the oral microbiome and oral health through the **National Health and Nutrition Examination Survey**. Such data may be used to inform review of tobacco product applications.

Novel Foods and Food Ingredients

Importance to FDA

Innovations in food ingredients and food production technologies provide consumers additional food choices and may improve public health, food productivity, and food security. Some of these ingredients and foods are new to the supply chain, and additional scientific information related to these new food ingredients is valuable. FDA conducts research about the safety, regulation, labeling, and use of these products to best protect consumers and make regulatory recommendations and decisions.

Examples

- FDA is working in cooperation with the U.S. Department of Agriculture to create a clear regulatory pathway for industry efforts to produce **foods made from cultured cells of animals**. In addition to evaluating the safety of new food additives or ingredients derived from this technology to ensure safety, FDA is considering review of compositional data for a variety of nutritive and non-nutritive constituents from a range of conventionally-sourced animal tissues to inform assessments of both identity and safety regarding products of this technology as compared to conventional foods. Availability of this information could potentially help support use of animal cell culture technology by industry to expand the food choices available to consumers.

- Scientific advancements in genome editing have led to the ability to more efficiently and precisely alter the genomes of food-producing organisms to provide desired traits. Such traits might otherwise only be achievable by laborious plant cross-breeding techniques, if at all. FDA has evaluated the safety of food from more than 180 varieties of genetically engineered plants and food from a genome-edited plant variety. If FDA's evaluation identifies safety or regulatory questions, the agency will request further information from developers to resolve them.

- Developed and validated a method to isolate *Salmonella sp*. from the increasing variety of plant-based meat alternatives on the commercial market, using Salmonella serotypes (*S. enteritidis* or *S. agona*) previously linked to plant-based protein ingredients. This project enhanced the agency's readiness to respond to potential future outbreaks associated with these novel food matrices.

Regenerative Medicine

Importance to FDA

Regenerative medicine refers to a general approach to restore, replace, or recreate cells, tissues, or organs to treat or mitigate disease. The types of products that FDA regulates in this category include cell therapy, therapeutic

tissue engineering products, any combination products using such therapies or products, some gene therapy products, and human cell and tissue products (except for those regulated solely under **section 361 of the Public Health Service Act**. Regulation of regenerative medicine therapies pose many challenges, some of which are listed below. FDA conducts research to improve and resolve challenges such as the lack of international consensus standards for regenerative product safety and effectiveness.

Examples

One example of a regenerative medicine therapy is a 3D-printed scaffold made of a new biomaterial with cells derived from allogeneic stem cells in vitro. Scaffolds allow multiple cell types to grow on a single implant to speed up tissue growth. This type of product raises scientific questions that affect regulatory evaluation and require evaluation by FDA researchers:

- The use of allogeneic stem cells may present compatibility issues between the living tissue and the 3D-printed implant or an immune response, such as inflammation.
- Product types cannot be sterilized in their final holding container (terminally sterilized), so it is a challenge to also assess sterility of the final product without compromising their structure and function.
- Methods are needed to predict whether the differentiated cells will revert to stem cells or create tumors.
- After implantation of this type of product, there are questions about whether the cells stay in place or migrate to other parts of the body where they may cause harm.
- Physics-based quantitative modalities are needed to assess the quality of regenerated tissue during and after product remodeling upon implantation.
- If the scaffold is designed to resorb (dissolve) at a rate proportional to cell proliferation, additional questions arise about the impact on scaffold structural integrity, biocompatibility of degradation products, cell survival and proliferation, and both structural and functional integrity of the regenerated tissue.

Advanced Manufacturing

Importance to FDA

Advanced manufacturing is a collective term for innovatively applied or new medical product manufacturing technologies and processes that can improve quality, enhance efficiency, address shortages of medical products, or speed time-to-market. Advanced production techniques often include one or more of the following characteristics:

1.) integrate novel technological approaches;
2.) use established techniques in a new or innovative way; or
3.) apply production methods in a new domain where there are no defined best practices or experiences.

The types of advanced manufacturing being applied to FDA-regulated medical products include but are not limited to the following:

- Additive manufacturing (also known as **3D printing**) increases manufacturing flexibility and personalization.
- Process intensification integrates, combines, or enhances steps in complex processes, making them more efficient, more reliable, and often shrinks the required space and resource requirements. There are examples across all medical product areas which include continuous manufacturing and modularization.
- Advanced manufacturing can apply smart manufacturing concepts that use automation, digitization, and artificial intelligence to streamline production methods, collect more process control data, and ultimately use a smart algorithm to adaptively control or make decisions about production or release. Advanced and smart manufacturing methods can be used across all medical products.
- Due to a combination of increased computing power,

improved cross-sectional imaging, and faster, more reliable additive manufacturing machines, a **new point-of-care manufacturing** medical specialty has emerged as evidenced by a significant increase in the number of hospital systems across the U.S. that have deployed various sizes of manufacturing capabilities. Also, advances in the intensification, and modularization of manufacturing platforms and facilities enable new opportunities for point-of-care manufacturing of therapeutics.

Examples

FDA supports and conducts research to encourage further development and adoption of advanced manufacturing technologies and evaluates products manufactured using these technologies, addressing several significant challenges:

- Rapidly scale manufacturing capabilities to respond more quickly to emerging threats and public health emergencies (e.g., **COVID-19**).
- Develop new approaches to facilitate rapid vaccine production, 3D printing, continuous manufacturing, and improved manufacturing approaches for a variety of cell-based and gene therapies (e.g., stem cells and chimeric antigen receptor T-cells, a type of immune system cell).
- Increase supply chain resilience to disruption by creating a flexible and agile network of small cost-efficient manufacturing sites that can pivot quickly to provide reserve capacity.
- Accelerate development of novel or patient-focused medical products by improving the robustness and cost-efficiency of manufacturing processes. For example, using 3D printing technology to develop standards for personalized drug-device combination hormone delivery systems (e.g., intravaginal rings) for menopausal women.
- Identify parameters influencing the production of stem cell products and gene therapy vectors using new, advanced manufacturing technologies.
- Accelerate availability of emerging therapies by enabling the rapid scale-up of processes for manufacturing and standards development, including for cell and gene therapies, supporting goals of the **21st Century Cures Act** (Cures Act, **Public Law 114-225**).
- Provide new tools to address medical product shortages often attributed to outdated manufacturing and control technologies and a lack of effective quality management systems.
- In fiscal years 2018 and 2019, FDA awarded grants under the Cures Act authority to fund extramural research fostering development of new technology in support of advanced manufacturing.
- Existing regulatory policies and recommended practices, standards, and industry-wide technical reports have been based on drug batch manufacturing processes. However, new technologies are focused on making drugs in a continuous process without isolated steps. In one of these studies, research is ongoing to better understand how to remove viral particles during the manufacture of protein biological products using the new continuous manufacturing (CM) paradigms. ICH Q5A principles need to be adapted to developing small-scale studies on CM's integrated continuous process steps, so FDA is investigating a commercially available continuous chromatography system and has developed a potential representative small-scale model for continuous viral filtration.

Increasing Access to Complex Generic Drug Products

Importance to FDA

The presence of generic drugs on the market helps to ensure availability of quality medicines at a lower cost to the American public.

FDA fosters the development of complex generic drug products in particular in our scientific work because complex products represent nearly one-third of brand drug products currently used but have less generic competition than non-complex drugs because they are

harder to genericize.

Some factors considered when determining whether drugs are complex include whether the products contain complex active ingredients, complex formulations/dosage forms, and/or are delivered through complex routes of delivery or with complex drug-device combinations. Evaluations of complex generic drug products often require advanced analytical technologies to properly assess quality attributes, critical and advanced quantitative methods, and modeling and data analytics methodology to establish scientific standards that would ensure therapeutic equivalence in patients. FDA prioritizes research to develop methods and approaches for establishing the sameness and bioequivalence of generic complex drug products with these and other factors in mind. Research on complex drug products informs FDA's development of guidance documents for industry addressed to generic drug developers, and review of applications.

Examples

FDA's scientific work on complex generics includes:

- Developing physiologically-based pharmacokinetic (PBPK) models for locally acting drugs and use of PBPK models to predict how formulation properties may affect the amount of drug available to have a therapeutic effect at a certain time after taking the drug.

- Applying quantitative clinical pharmacology approaches to address multiple challenges in bioequivalence studies, including defining appropriate standards for narrow therapeutic index (NTI) drugs and determining appropriate comparative clinical endpoints when needed. NTI drugs are products where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity.

- Evaluating advanced analytical technology to enhance the information content (e.g., improved precision and accuracy) of data used to compare complex generics to their reference listed drugs. Using improved analytical technology for complex drugs with many attributes results in improved sensitivity and resolution and provides additional means to support a determination that generic versions are bioequivalent to the reference product.

- Identifying alternatives to comparative clinical endpoint bioequivalence studies for evaluating the bioequivalence of products containing certain locally acting oral drugs. FDA is currently conducting a study to validate use of an alternative approach for comparing canine oral dosage forms containing both locally and systemically acting active pharmaceutical ingredients. The results of this study will impact pre-approval generic animal drug applications and the evaluation of post-approval formulation changes for innovator and generic animal drug products.

- Establishing the Center for Research on Complex Generics (www.complexgenerics.org) to increase access to safe and effective complex generic drug products through collaborative research, training, and exchange. The center facilitates communication and information sharing among FDA, academia, and generic drug companies. It also will make complex analytical assays and pharmaceutical development expertise accessible to the generic industry to support more efficient development of high-quality complex generics.

Medical Product Development Tools

Publicly available, FDA-qualified, medical **product development tools** facilitate industry's ability to harness innovative science and technology. These tools, methods, and models are used to reduce the time, complexity, or cost of developing FDA-regulated products, while increasing the reliability and robustness of the results used to support product development.

Biomarkers

Importance to FDA

Biomarkers are characteristics that are objectively measured as indicators of health, disease, or a response to an exposure or intervention, including therapeutic interventions. Biomarkers are useful to medical product

developers and FDA for uses such as:

- Identification of a biomarker that may lead to improved diagnosis of a disease or predict future disease severity or outcomes. Examples include blood pressure measurements as an indicator of cardiovascular risks, or measurements of blood sugar in diabetes.

- Identification of biomarkers that may lead to improved understanding of the impact to tobacco products.

- Biomarkers can be used to identify and evaluate the effectiveness of medical or veterinary treatments or devices, monitor the safety of a therapy, and evaluates whether a treatment is having the desired effect on the human or animal body.

- Biomarkers can play a critical role in bridging non-clinical results to clinical research and identifying patient populations susceptible to adverse effects of or those responsive to medical treatments (also known as Precision Medicine.)

FDA and medical product developers are interested in developing novel biomarkers to use in product development and/or evaluation to improve accuracy and efficiency of clinical trials. FDA has a **biomarker qualification** program for new biomarkers aimed to enable understanding of how a biomarker may be applied in a specific context of use. Qualified biomarkers have the potential to provide valuable information that may promote innovation and reduce uncertainty in regulatory decisions during drug development. When a biomarker is *qualified*, it means that the biomarker has undergone a formal regulatory process to ensure that FDA can rely on it to have a specific interpretation and application in medical product development and regulatory review, within the stated context of use. It is important to note that the biomarker can be qualified and not the biomarker measurement method.

The **Biomarkers, Endpoints, and other Tools** resource is a living document developed jointly by FDA and the National Institutes of Health (NIH) to promote consistent use of biomarker terms and concepts, and thereby advance biomarker science. This resource clarifies terminology and uses of biomarkers and endpoints as they pertain to the progression from basic biomedical research to medical product development to clinical care.

Examples

FDA research is advancing the development of novel biomarkers:

- Identifying biomarkers of tobacco exposure such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) that are informative for assessing potential health risks of tobacco products in the review of pre-market and modified risk tobacco product applications.

- Identifying and evaluating immune correlates of protection for many pathogens of public health concern. Immune correlates of protection serve as a biomarker of effectiveness for vaccines.

- Identifying more sensitive markers of drug-induced cardiac (heart) injury and liver injury, as well as developing in vitro and in vivo tests for assessment of treatment-induced genetic damage.

- Exploring biomarkers to assess patient reactions to metal implants and susceptibility to hypersensitive and chronic immune responses to promote device safety.

- Collaborating in a number of studies, including but not limited to, research in diagnostic biomarkers of traumatic brain injury and kidney injury, and biomarkers of tobacco exposure and potential harm as documented in the **FDA-NIH Population Assessment of Tobacco and Health Study**.

- Analyzing new measures of tumor response and progression developed specifically for cancer immunotherapies (e.g., iRECIST) through pooled analyses of oncology clinical trial data submitted to FDA. These new measures of tumor response were designed to capture atypical responses seen with immunotherapies (e.g., an initial increase in tumor size followed by a clinically important reduction in

tumor burden or initial reduction in tumor size with the appearance of new lesions that subsequently regress), but there is limited evidence to support whether the new measures better assess patient outcomes.

- FDA qualified total kidney volume (TKV) as a prognostic biomarker to predict the rate of loss of kidney function in the orphan disease autosomal dominant polycystic kidney disease. Subsequently, the clinical review division accepted TKV as a reasonably likely surrogate endpoint for drug approval under accelerated approval thereby substantially shortening the required duration and size of Phase 3 trials.

Novel Technologies to Improve Predictivity of Non-clinical Studies and Replace, Reduce, and Refine Reliance on Animal Testing

Importance to FDA

Animal studies are frequently used to assess certain aspects of risk, toxicity, activity, or public health impact of FDA-regulated products that focus on a product's nature, chemistry, effects (pharmacology), and its potential damage to the body (toxicology). FDA is working to replace, reduce, and refine (the 3 Rs) dependence on animal studies by advancing development of, and evaluating new, fit-for-purpose non-clinical tools, standards, and approaches that may someday improve predictability. In some cases, in silico modeling, such as using available information in computational science approaches to predict safety issues, can be used to supplement and may potentially replace some risk analyses that are currently based on animal data. FDA uses non-clinical and clinical data to assess the products it regulates. The predictive value of current non-clinical testing approaches varies. Sometimes clinical evaluations identify risk and safety concerns that were not predicted by current non-clinical methodologies. Therefore, the development of tools with improved predictive value may enable FDA to make informed decisions about clinical investigations, licensures, and other all FDA regulated products such as food, cosmetics, and tobacco.

The development and eventual availability of **new alternative methods** may more accurately identify, predict, evaluate, and reduce the degree and likelihood of risks of FDA-regulated products. In addition to enhancing safety, this could also help speed development and reduce costs in assessing new FDA-regulated products, leading to improved health outcomes. Systematically assessing and comparing the information from alternative methods with traditional methods offers an opportunity to evaluate the applicability and predictability of the new approaches and their ability to support FDA's regulatory mission of safeguarding public health.

Examples

- Developmental neurotoxicity tests are needed especially for sensitive populations such as infants and children. Neurotoxicity occurs when the nervous system (e.g., brain) is purposely or accidentally exposed to toxic substances such as chemotherapy, lead, and mercury. FDA is actively exploring alternative methods such as using in vitro cultures of developing brain stem cells since there is no currently established predictive in vitro neurotoxicity assay that allows correlation to neurodevelopment in pediatrics.

- FDA participates in large multi-laboratory studies to assess the reliability, sensitivity, specificity, and reproducibility of in vitro alternatives to in vivo assays (e.g., to assess potency of certain vaccines).

- The Open Online Simulations for Stimulating Peripheral Activity to Relieve Conditions (**o²S²PARC**) accelerates the availability of safe and effective neuro-prosthetics. FDA developed a freely accessible online platform that enables developers to simulate modulation of the peripheral nervous system and its impact on organ physiology using validated models and state-of-the art in silico tools.

- Investigators in multiple centers are working with microphysiological systems either produced commercially, in house, or by academics to assess their performance and applicability to toxicity and activity assessment.

- FDA, through the International Cooperation on Cosmetics Regulation (ICCR), has been involved in numerous activities to address **new alternative**

methods (MAMS) to assess cosmetic safety.

Model-Informed Product Development

Importance to FDA

Model-informed product development (MIPD) aims to integrate information from diverse data sources to help decrease uncertainty and lower failure rates, and to develop information that cannot or would not be generated experimentally. MIPD encompasses model-informed drug development (MIDD), an approach that involves developing and applying exposure-based biological and statistical models derived from preclinical and clinical data sources to inform drug development or regulatory decision-making. FDA's **MIDD Pilot Program** facilitates integrating MIDD into more drug applications and advancing its use, and addresses some of FDA's goals under the **Prescription Drug User Fee Act VI (PDUFA VI)**, included as part of **FDA Reauthorization Act of 2017 (Public Law 115-52)**.

MIDD applications include potential contributions toward predicting clinical outcomes; informing clinical trial designs and efficiency; supporting evidence for efficacy; optimizing drug dosing/therapeutic individualization; predicting product safety and evaluating potential adverse event mechanisms; product performance optimization; and informing policy.

FDA has committed resources to transforming computational modeling from a valuable scientific tool to a valuable medical device regulatory tool and to developing mechanisms to rely more on digital evidence. FDA continues to advance these methodologies and techniques to ensure the benefits of product innovation and more rapid introduction of life-saving technology to our nation's patients.

MIPD applies to innovations in processing of foods, which rely on modeling and simulation to ensure foods are safe and wholesome for consumption. Using modeling and simulation-based approaches helps to examine situations that cannot easily be studied experimentally, such as retroactive studies of foodborne outbreaks or contamination events; prospective studies of intended or unintended changes in the food safety or nutrition system (e.g., food, environment, processing, handling, consumption, or compliance); or system sensitivity and vulnerability assessments.

Mathematical models developed using modeling and simulation-based approaches evaluate specific conditions to study systems based on different levels of exposure, chemical toxicities, growing, harvesting, or processing practices, levels of compliance with **Good Agricultural Practices**, **Current Good Manufacturing Practices**, **Food Code**, or other regulations, proposed mitigations or controls and various failure/outbreak scenarios. Applying modeling approaches to food processing improves risk assessment of pathogens and toxins in foods and predicting risks of illness in food categories. Compliance activities rely on modeling to inform regulatory decisions and to ensure regulated stakeholders meet legal requirements. In addition, **FDA's Catalog of Regulatory Science Tools** collates innovative science-based approaches to help improve the development and assessment of emerging medical technologies. Tools in the catalog include phantoms, methods, and computational models and simulations.

Examples

FDA advances the use of modeling and simulation in product development:

- Evaluating dose selection and refinement, treatment duration, response measures, safety evaluations and assessing the combined effect of drug interactions, kidney and liver failure in patients in the absence of dedicated trials.

- Developing means to facilitate software development that assists in analyzing medical imaging and diagnostics. For example, FDA developed the **Virtual Imaging Clinical Trials for Regulatory Evaluation (VICTRE)** multi-modality anthropomorphic breast phantom. VICTRE is a digital breast phantom with modifiable parameters, including phantom voxel size (resolution) and breast density in the area of medical imaging and diagnostics.

- Making available **The Virtual Family**: A set of anatomically correct whole-body computational models based on multimodal imaging.

- Credibility of Computational Models Program: Research on Computational Models and Simulation Associated with Medical Devices

- **Developing multiple (Quantitative) Structure-Activity Relationship models** that use a range of in silico tools to predict toxicological outcomes, such as genotoxicity, carcinogenicity, and drug-induced liver injury. Other research will explore additional model endpoints and expand previous models with newly published data.

- Using many in vitro techniques to identify drug–drug interactions and drug–target interactions that may be clinically relevant. For example, patch clamp techniques evaluate the effects of drugs on cardiac ion channels and provide physical evidence of drug interactions with a variety of transporters, enzymes, and receptors that may be used in regulatory decision-making.

- Developing mechanistically informed models based on pharmacokinetics that predict the disposition of chemicals, medical products, and their metabolites in the body and could be used for examining their potential for biopersistence.

- **Projecting population level effects** of a potential public health standard (i.e., nicotine standard) on the prevalence of tobacco use, tobacco-related mortality, and life-years gained.

- With respect to cosmetics, an **approach** of combining predictive computer modeling and *in vitro* test methods has been developed in order to minimize animal testing when evaluating skin sensitization potential of cosmetic ingredients.

Unleashing the Power of Data

Introduction

Data are a critical resource for all of FDA's work. Unleashing the power of data refers to identifying and using reliable data sources, some of which may represent large, complex data sets requiring improved analytics, and in some cases, harnessing high-performance computing environments and new computational tools based on artificial intelligence (AI). FDA is working to obtain more and higher-quality data, be more proactive in gathering data, be more creative in analysis and interpretation, to support regulatory decision making in different aspects of the lifecycle of regulated products.

The healthcare system generates an abundance of clinical care data that can potentially be harnessed to inform regulatory decision making. These health data include but are not limited to data from electronic health records (EHRs), medical imaging, genomic sequencing, pharmacy dispensing, payor records, pharmaceutical research, digital health technologies (DHTs), and medical devices.

The breadth, depth, and diversity of these data can help fill knowledge gaps related to product safety, effectiveness, and risk reduction. Insights gained from data are balanced with subject matter expertise to make decisions and draw conclusions, especially when unique data features and potential limitations may give rise to misinterpretations and conflicting conclusions in clinical studies.

FDA uses healthcare data and analytics to improve the quality and integrity of FDA-regulated products throughout the product lifecycle. Rapid collection and analysis of quality data can help fill knowledge gaps and inform FDA regulatory decision-making. FDA is interested in developing new approaches to harnessing these data to improve regulatory decision-making and more effectively connect today's groundbreaking scientific discoveries with the rapid development and approval of new FDA-regulated products. FDA can also increase the knowledge of patients and consumers who must make informed decisions about FDA-regulated products.

Product Safety Surveillance

Importance to FDA

FDA receives many reports about safety or effectiveness of FDA-regulated products each year. For many FDA-regulated medical products, due to limitations of pre-market clinical investigations (e.g., size, follow-up timing, included populations), safety data often need to be continuously collected postmarket. Postmarket adverse events may affect regulatory decision-making and actions, such as requiring safety-related labeling changes and issuing safety communications. To protect the health of the public, it is important for FDA to identify potential safety signals as early as possible using postmarket surveillance. To evaluate a safety signal, it may be necessary to understand the mechanisms that may underlie the observations and, in some cases, conduct or request additional clinical and epidemiological studies.

FDA is working to improve ways to identify new safety signals with increased precision in decreased time. Some of the approaches being evaluated for feasibility rely on incorporating artificial intelligence (AI), **real-world evidence (RWE)**, and leveraging data from a combination of active and passive safety surveillance systems listed below.

- The **FDA Sentinel System** (Sentinel) is an active surveillance system that uses routine querying tools and pre-existing electronic healthcare data from a distributed data network to detect safety signals and evaluate the safety of FDA-regulated medical products.

- The **Biologics, Effectiveness and Safety (BEST)** system, is an active surveillance system

which builds and expands upon activities undertaken as part of previous FDA collaborative studies for biologic product safety and effectiveness. BEST is a multi-site set of databases that accrues data on over **100 million individuals** and uses a distributed data network, a common data model, data curation, and different types of analytical tools.

- **MedWatch** is the FDA's medical product safety reporting program for health professionals, patients, and consumers. MedWatch receives reports from the public and when appropriate, publishes safety alerts for FDA-regulated products such as: prescription and over-the-counter medicines, biological products, medical devices, combination products, special nutritional products such as dietary supplements, cosmetics such as moisturizers and shampoos, and food such as beverages and ingredients added to foods.

- The **FDA Adverse Event Reporting System** is a passive reporting database for healthcare professionals, patients, consumers, manufacturers and others to report adverse events, medication errors, and product quality complaints. The database is designed to support the FDA's post marketing safety surveillance program for drug and therapeutic biologic products.

- The **Vaccine Adverse Events Reporting System** is a passive reporting database administered by FDA and Centers for Disease Control and Prevention (CDC), that contains adverse event reports associated with licensed vaccines.

- FDA uses the **Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System** to receive reports of adverse events (AEs) and product complaints (PCs) pertaining to FDA-regulated foods, dietary supplements, and cosmetic products.

- Through the **Safety Reporting Portal**, FDA gathers information from the public (e.g., consumers, healthcare professionals, manufacturers) on the risks, problems, or unexpected health issues related to pre-market or marketed human drugs and biologics, human or animal foods, animal drugs, tobacco products, and dietary supplements.

- **FDA Manufacturer and User Facility Device Experience Database (MAUDE)** contains reports of adverse events involving medical devices.

- The **Medical Product Safety Network (MedSun)** is an adverse event reporting program which fosters an important partnership between clinical sites and FDA

- The **National Evaluation System for health Technology (NEST)** is a voluntary data network of collaborators able to efficiently consolidate Real-World Evidence (RWE) from clinical registries, electronic health records, medical billing claims, patient-mediated data, and other sources to inform medical device development and evaluation, and to support regulatory decision-making throughout the total product lifecycle (TPLC).

Examples

FDA develops and uses multiple techniques to monitor for known and identify new potential safety concerns.

- Evaluating spontaneous adverse event reports (including medication errors), disease and product exposure registries, and pharmacoepidemiology and human factors studies. Other approaches include developing databases and analyzing platforms that incorporate information from the FDA Adverse Event Reporting System reports, literature, poison centers, toxicology reports, drug use data, and Sentinel.

- Evaluating device related adverse event reports submitted through the MDR and MedSun reporting systems for medical devices, condition and product-related device registries and registry networks, the National Evaluation System for health Technology (NEST), mandated post market studies, and the medical literature to assess for new device performance issues. In addition, developing artificial intelligence and machine learning (AI/ML) platforms to surveil FDA databases and public

sources for relevant potential safety issues.

- Leading several studies, as part of Sentinel, in response to the COVID-19 pandemic. Literature has suggested that patients with COVID-19 may be at risk of developing thromboembolic complications (e.g., movement of a blood clot to a secondary location), although there is a knowledge gap on the incidence, determinants, and consequences of these events. FDA is leading an **epidemiologic study** with the Sentinel System to assess the frequency of arterial and venous thromboembolic events and their consequences among patients with COVID-19 and evaluate risk factors for these events. This information will help to inform thromboprophylaxis strategies for reducing the risk of these adverse outcomes.

- Investigating data submitted through the **Reportable Food Registry** enables FDA to partner with industry and U.S. states to investigate and mitigate risks associated with adulterated food products, so that corrective actions can be quickly implemented.

- New analytical methods developed by FDA for detection of the carcinogen NDMA in ranitidine drug products indicated actual levels were much lower than previously reported. A randomized clinical trial was conducted and showed that ranitidine does not convert to NDMA in humans. In addition, supporting in vitro experiments that simulated human gastric fluid also showed that ranitidine did not convert to NDMA under physiological conditions. Based in part on this research, FDA may consider allowing ranitidine-containing products back on the market if they are proven to be stable, with low, acceptable amounts of NDMA that do not increase during storage.

Diverse Data and Technologies

Artificial Intelligence

Importance to FDA

Artificial intelligence (AI) solutions have the potential to improve automation and *learning* of medical devices, the efficiency of diagnostic/therapeutic development and commercial manufacturing, regulatory assessment, and postmarket surveillance, among many other potential applications. These improvements increase the accuracy of predictive modeling, enable efficient automation of medical devices and manufacturing processes, leverage knowledge management resources to improve regulatory review, and focus and improve postmarket surveillance. FDA views AI as encompassing continued improvement in code and infrastructure.

To achieve and promote efficiencies within FDA and in industry, FDA aims to improve its understanding of AI's potential and limitations. Considerations include the technical and practical application of AI, new regulatory questions introduced by AI applications, and the impact of AI solutions across the lifecycle of FDA-regulated products.

Examples

FDA advances the understanding and use of AI to support a diverse set of needs related to FDA-regulated products, including:

- Exploring the use of machine learning (ML) algorithms to:
  - Target high-risk seafood products offered for import;
  - Detect adverse events in different data sets, including post market data; and
  - Study the effects of using synthesized data sets for training and testing in both pre-market testing and the FDA-regulated product lifecycle; and
  - Predict the time to first submissions for abbreviated new drug applications (ANDA) referencing new chemical entities to inform the Agency's ANDA workload and prioritize research.

- Evaluating the potential impact of natural language processing (NLP) systems to automatically identify and International Council for Harmonization Medical Dictionary for Regulatory Activities (MedDRA) code adverse events mentioned in product labels. The labeled status of the MedDRA-coded adverse events in product labels facilitate the triaging and review of the adverse events described in individual case safety reports (ICSRs) submitted to the FDA Adverse Event

Reporting System (FAERS).

- Conducting **research** on AI/ML-based medical devices:
  - Data augmentation, transferring learning, and other novel approaches to enhance AI/ML training/testing for small clinical datasets.
  - Study design and analysis methods for AI/ML-based computer-aided triage (CADt).
  - Non-clinical phantoms and test methods for assessing specific imaging performance claims for DL-based denoising and image reconstruction algorithms.
  - Imaging phantoms and computational models to support QI and radiomics assessment.
  - Assessment techniques for evaluating the reliability of adaptive AI/ML algorithms to support non-clinical test method development.
  - Assessment approaches to estimate and report the robustness of AI/ML to variation in data acquisition factors.
  - Technical factors influencing AI reproducibility for digital pathology applications.
  - Methods for assessing the generalizability of AI performance in digital pathology applications
- Investigating the potential of AI to improve the efficiency of reviewing regulatory submissions. For example, FDA applies natural language processing to regulatory submissions to classify its relative complexity.
- Studying how AI can combine diverse data so clinical trial results can be analyzed in a more comprehensive and expeditious way.
- Applying AI to support the processing and evaluation of individual case safety reports submitted to FAERS) and VAERS by leveraging NLP, ML, and visualization techniques to facilitate efficient FAERS data analyses.
- Exploring how AI can be used in pharmacometrics, the science that quantifies drug, disease, and trial information, to aid efficient drug development, and/or regulatory decisions.
- Exploring how AI can be used to advance precision medicine, by predicting patient responses based on baseline patient characteristics.
- Developing standardized ontology-based metadata to leverage WGS data to predict source tracking regarding domestic animal host of food source. These metadata ontologies also support risk assessment tools such as **GenomeGraphR**, a user-friendly open-source web application for foodborne pathogen WGS data integration, analysis, and visualization.
- Designing and delivering workshops to introduce AI and ML to FDA staff and showcase how AI and ML can be applied to FDA's regulatory landscape. Workshops such as this enhance the knowledge base of our inspectional cadre, keeping them attuned to how these emerging technologies may impact their investigations.
- Using ML to develop computer models that use genomic data to predict the mean inhibitory concentration (MIC) for pathogens and antimicrobials surveyed for the National Antimicrobial Resistance Monitoring System (NARMS). The goal is to develop reliable methods to predict MICs from whole-genome sequence data
- Conducting educational Al and ML workshop through the CERSI program on potential causal inference, focusing on heterogeneous effects, complex data structures, interpretability and explainability of AI results.
- Researching image blending to expedite development and performance assessment of mammographic computer-aided diagnostic (CAD) devices. The goal of this **work** was to reduce the data burden for medical device manufacturers and to provide information to inform review of mammographic CAD systems.

- Designing a statistical framework that would be robust to distributional shifts over time for **software as a medical device (SaMD)** adapting in the real world to ensure the safety and effectiveness of potential artificial intelligence/machine learning (AI/ML)-based SaMDs under a CERSI research project.

- Developing a framework with a CERSI partner for measuring robustness of ML models to contextual changes in the real-world data and inform regulatory decision-making by categorizing which contextual factors matter for a particular intended use and how to better define the context of appropriate use.

- Exploring how AI is used during commercial drug manufacturing to improve quality decision making

Digital Health Technologies

Importance to FDA

Digital health technologies (DHTs) are systems that use computing platforms, connectivity, software, and/or sensors for healthcare and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, with, or as an adjunct to other medical products (devices, drugs, and biologics). They may also be used to develop or study medical products. Some DHTs may meet the definition of a medical device, while others do not. The FDA **Digital Health Center of Excellence** serves as a resource for internal and external stakeholders to accelerate advancements in digital health. Furthermore, the DHCoE coordinates Agency-wide digital health work, providing regulatory advice and supporting regulatory review of DHTs.

DHTs are helping to move healthcare from the clinic to patients by improving understanding of patient behavior and physiology outside traditional clinical settings and potentially enabling early therapeutic interventions. DHTs, such as sensors and other telehealth technologies, provide important opportunities in clinical trials to gather information directly from patients at home (decentralized clinical trials), and to gather data more frequently or continuously as they go about their lives. DHTs using advanced algorithms may be susceptible to errors or bias, which may lead to malfunction or misinterpretation of health data. Therefore, regulatory science tools and methods, such as simulations to test algorithm performance, need to be developed to protect data integrity, promote health equity, and improve overall reliability of DHTs.

Examples

- FDA is developing non-clinical assessment methods to evaluate electrocardiogram (ECG) analysis algorithms under noisy conditions, representing real-life device use scenarios. ECGs record the electric signal from the heart and can be used to diagnose abnormal heart rhythms such as atrial fibrillation. This study may enable device manufacturers to gain meaningful performance estimates of their ECG analysis algorithms, especially when such algorithms use inputs from DHTs.

- FDA established a **Medical Extended Reality Program under which to conduct research on medical extended reality-based medical devices**, in addition to activities in the **Patient Monitoring and Control Program: Research on Patient Monitoring and Control Devices**.

- Scientific evaluation of the sources of variability in smartphone- and smartwatch- based wearable sensors in **Human-Device Interaction Program: Research on Human Interaction with Medical Devices | FDA**

- FDA is collaborating with CERSIs to study the use of DHTs (actigraphy) in patients with heart failure and in children with depression. Actigraphy monitors cycles of human activity and rest using a wearable watch-like instrument. These studies may support the use of DHTs in the evaluation of new drugs for heart failure and depressive disorders.

- FDA and NCATS/NIH built a mobile application and website called CURE ID allowing healthcare providers globally to share and communicate information about the use of existing drugs in clinical practice in new ways (“repurposing”) — including in pregnant patients to treat cancer and infectious diseases such as COVID-19. The CURE Pregnancy

Treatment Repository application is gathering data on drugs used during pregnancy to expand our knowledge about their effects in pregnant women.

Use of Real-World Evidence to Support Medical Product Development and Regulatory Decision-Making

Importance to FDA

Real-world data (RWD) are data relating to a patient's health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records (EHRs), medical claims, registry, patient-generated data, and data gathered from mobile devices and other digital health technologies (DHTs). Real-world evidence (RWE) refers to clinical evidence about the usage and potential benefits or risks of an FDA-regulated product derived from analysis of RWD.

In addition to the Agency's use of the **FDA Sentinel** and **Biologics Effectiveness and Safety (BEST)** systems, FDA is collaborating with the Medical Device Innovation Consortium (MDIC) to build the National Evaluation System for health Technology (**NEST**) with the purpose of driving the improvement of quality and efficient use of RWD to inform medical device development and evaluation throughout the entire product life cycle. The NEST coordinating center (**NESTcc**) helps researchers quickly access, link, and synthesize data from different sources across the medical device landscape.

Recognizing the potential value of RWD, FDA is committed to exploring the use of **RWE in regulatory decision-making**, including its ability to provide fit-for-purpose clinically meaningful information about the safety and effectiveness of drug and biological products. As part of its efforts under the **21st Century Cures Act** (**Public Law 114-225**), FDA established the **RWE program** to explore the use of RWE in regulatory decision-making. As a result, FDA has published draft guidance and launched supporting projects that will provide insight into how RWD and RWE can play a role in supporting the evaluation of the safety and effectiveness of drug and biological products.

Examples

FDA is advancing use of RWE in several ways:

- Funding RWE demonstration projects, including **Randomized Controlled Trials Duplicated using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology (RCT-DUPLICATE)**. RCT-DUPLICATE attempts to duplicate the results of recently completed randomized controlled clinical trials relevant to regulatory decision-making using RWE, based on health insurance claims data.

- Funding the Source Data Capture from Electronic Health Records (EHRs): Using Standardized Clinical Research Data (OneSource) Project. OneSource is a collaboration between investigators at the University of California, San Francisco (UCSF), Stanford University and FDA. The goal of this project is to develop methods and tools to automate the flow of structured EHR data into external systems and thereby reduce operating costs, save time, and improve data quality for clinical trials. The OneSource project provides an approach to transmit structured data from the UCSF EHR system to a clinical trial electronic data capture (EDC) system. In this approach, the Electronic Case Report Forms (eCRFs) for a phase II clinical trial, (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And molecular Analysis 2 (I-SPY 2 TRIAL)) are populated. OneSource leverages standards from Health Level 7 (HL7) and Clinical Data Interchange Standards Consortium (CDISC) for the capture and transmission of clinical research data.

- Participating in studies focused on understanding how RWD may be able to inform regulatory decisions. One objective is to facilitate the use of RWD to learn about the safety and efficacy of FDA-approved oncology drugs in populations generally under-represented in clinical trials and exploring the potential use of real-world endpoints of response and progression.

- Using the BEST system and health insurance claims data in collaboration with the U.S. Centers for Medicare & Medicaid Services to evaluate the effectiveness of annual influenza vaccines.

- Collaborating with NESTcc to generate evidence across the medical device product lifecycle by leveraging RWE and applying advanced analytics to data tailored to the unique data needs and innovation cycles of medical devices.

- Supporting projects exploring analytic methods that inform RWE, such as Targeted Maximum Likelihood Estimation, for drawing conclusions between the occurrence and causes of an event (i.e., causal inference).

- Conducting projects through the Sentinel **Innovation Center**, that incorporate data science innovations such as natural language processing and machine learning to expand access to and use of electronic health record data for medical product surveillance.

- Awarding funding for four FDA cooperative agreement grants (from among 31 applications) to explore the use of RWD in generating RWE for regulatory decision-making.

- Evaluating how to use novel data sources to obtain better marketplace, safety, and quality data on **cannabis-derived products including cannabidiol (CBD)** to help inform regulatory policy development.

- Assessing disparities in occurrence and outcomes of adverse drug events in minority populations using real world administrative claims and EHR.

- Assessing the association between baseline patient characteristics (e.g., organ impairment) and patients outcomes using EHR data.

Empowering Patients and Consumers

Introduction

FDA is developing new ways to engage patients and consumers to better understand the American patients' and the public's perspectives and preferences including related to outcomes. The scope of products regulated by FDA affects consumers and patients, including the veterinary client-patient relationship (VCPR). Understanding patient, consumer, and VCPR perspectives and preferences including related to outcomes enables FDA to understand what matters most in new treatments and develop targeted and easy-to-understand communications and resources to empower the diverse American public to make better informed decisions. If consumers, patients, caregivers, and healthcare professionals become more informed about the products FDA regulates, they can live healthier and more productive lives.

Patient and Consumer Preferences and Perspectives

Importance to FDA

Personal preferences and perspectives influence how patients and consumers make decisions to use medical products, tobacco products, or participate in treatment. FDA encourages medical product sponsors to collect and submit patient and consumer perspectives (e.g., patient preference information (PPI)). The Agency collects, measures and analyzes this information to help inform how it considers benefit–risk tradeoffs related to medical products for patients with a specific disease or condition, or identifies subpopulations with heterogeneous preferences.

Patients' direct experience living with a disease and the available treatments, as well as the values, beliefs, attitudes, and cultural factors of consumers, patients, caregivers, and healthcare practitioners play an important role in both regulated industry's product development and FDA's regulatory decision-making. The Agency uses qualitative and quantitative social and behavioral data from various sources, such as regulatory submissions, research studies, and other specific outreach programs to inform pre- and postmarket decisions and regulatory policy.

FDA seeks to understand the benefit and risk tradeoffs acceptable to the patients who are using medical products and examines consumer understanding of risk statements regarding tobacco products. This includes consideration of the burden of disease and treatment on patients and their caregivers, identifying patients' unmet needs related to disease treatment, and in the case of tobacco products, understanding the impact of tobacco product use and exposure to tobacco emissions by non-users.

Examples

FDA engages patients and consumers in the following ways:

- Conducting small, informal, non-regulatory, non-public **Patient Listening Sessions**, where patients directly share their experiences with a disease or condition with FDA staff. FDA, patients, caregivers, and advocates discuss a variety of topics, including: impact on daily activities, priorities to consider when developing medical products, and aspects related to clinical trial recruitment and participation.

- Conducting public **Patient-Focused Drug Development Public Meetings** to obtain patients' perspectives on specific diseases and their currently available treatments from a broader representation of the patient/disease community. These meetings have a systematic format designed to engage patients and elicit their perspectives on two topic areas: (1) the most significant symptoms of their

condition and the impact of the condition on daily life; and (2) their current approaches to treatment, as well as questions posed by FDA review staff to better understand patients' perspectives on their disease, treatments, and clinical trials.

- Collecting perspectives from patients in cancer clinical trials of undesirable and harmful symptoms to help other patients and healthcare professionals evaluate potential side effects of anti-cancer therapies.

- Developing strategies for increasing and improving patient engagement in medical product development. The Patient Engagement Collaborative (PEC) is a partnership between the FDA and the Clinical Trials Transformation Initiative (CTTI). The members of the PEC share their experiences and discuss ways to enhance patient engagement to include patient perspectives in the medical product development process and regulatory discussions at the FDA.

- Collaborating with the **Medical Device Innovation Consortium**, a public–private partnership, to explore the impact of patient selection methods (e.g., patients with a confirmed diagnosis from a licensed healthcare professional versus an online panel) on the evaluation of the benefit–risk tradeoffs that people living with heart failure are willing to make for new heart failure devices.

- Measuring PPI for investigational or novel treatments, such as gene therapy for sickle cell disease and osteoarthritis of the knee, and islet cell transplantation (when insulin-producing pancreas cells from a donor are transferred to a person with diabetes) for hard-to-control type 1 diabetes. PPI data provide FDA with information about patients' benefit–risk tradeoff tolerance. This is particularly important for medical products that may offer benefits and risks that may not be well understood due to a small number of patients in clinical trials with limited follow-up time.

- Supporting research studying how risk claims of new tobacco products entering the market affect consumers' judgments and intended behaviors. The research evaluates how likely nonusers (including youth and other vulnerable populations) would be to start using tobacco products, and how likely current adult users would be to transition to potentially less harmful products or stop using them altogether.

- Preparing a **curriculum for teachers** to educate middle and high school students regarding dietary supplements. This curriculum includes a broad range of topics impacting consumers including adverse event reporting; live microbials (commonly referred to as "probiotics"); athletic performance enhancement/bodybuilding products; and dietary supplement labeling and advertising.

Patient-Reported Outcomes and other Clinical Outcome Assessments

Importance to FDA

FDA increasingly looks to patients to understand how patients describe their health status, because patients are the experts in living with their disease or condition. Input from patients or their caregivers about what is important can then be used to select or develop tools to measure what matters most to patients. Clinical outcome assessments (COAs) may capture outcomes that are important to patients, such as how they feel or function or how long they survive. They play a central role in ensuring that what matters to patients is factored into regulatory decision-making. The **21st Century Cures Act** (Cures Act, **Public Law 114-225**), defines *clinical outcome assessment* as "(A) a measurement of a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions; and (B) includes a patient-reported outcome."

There are different types of COAs. While each COA should focus on the patient, they provide a different perspective on a patient's health status.

- Patient-reported outcomes (PROs): measures of a patient's health status as reported directly from the patient without added interpretation by a healthcare worker or anyone else, such as a pain scale.

- Clinician-reported outcomes: reports coming from a trained healthcare professional regarding their interpretation of signs or behaviors that can be observed related to a patient's disease or condition.

- Observer-reported outcomes: assessments of observable signs, events, or behaviors related to a patient's health condition as reported by individuals who observe the patient in daily life, like parents or caregivers.

- Performance outcome assessments: measurements collected when a patient is asked to complete a well-defined, repeatable, and standardized task, such as reading an eye chart or performing a walking test.

Strengthening FDA's ability to use patient-focused methodology to inform regulatory decision-making is specified in **FDA user fee agreements** for medical product development and the Cures Act. FDA increased knowledge and experience by performing research that informs the development and refinement of COA measures to support regulatory decision-making.

Examples

FDA advances the development of COAs, including PROs, through the following:

- Implementing a pilot grant research program supporting the development of publicly available core data sets of COAs and their related endpoints for specific disease indications, including PRO measures for migraine, and observer-reported outcome measures for acute pain in infants and young children. The program also supports the development of a core set of COAs (potentially including both performance outcome measures and PRO measures) to assess the full range of physical function severity with potential generalizability across a range of conditions.

- Working with academia to evaluate whether previously developed PRO measures perform differently in people living with heart failure from different demographic groups (such as racial and ethnic groups, gender groups, children, and literacy levels). FDA is exploring how these instruments may be modified to adequately capture symptoms in diverse patient groups. These PRO measures could be used to inform pre-market approvals and postmarket surveillance efforts.

- Collaborating with professional organizations to develop novel PRO measures that measure symptoms patients may experience following placement of artificial lenses. Collecting this information in a structured way is useful for clinical studies on artificial implantable lenses.

- Supporting the study of severe mental illness and suicidal ideation and behavior by supplementing existing **FDA Sentinel System** data with PRO measures. PRO measures are collected through validated depression, anxiety, alcohol use, and drug use surveys used in mental health specialty and primary care clinics. The PRO measures are used to develop models to predict suicidal behaviors for use in future observational research and trials.

Empowering Patients and Consumers to Make Better-Informed Decisions

Importance to FDA

Application of social and behavioral science (SBS) research is intended to provide patients and consumers with appropriate information to help them make decisions about the use of FDA-regulated products. SBS research guides the development of evidence-based messaging and information; evaluates the impact of communication and educational materials; and strives to understand beliefs and attitudes of diverse patient and consumer audiences.

Developing clear, science-based communications empowers patients, healthcare professionals, and consumers to make the best decisions possible about FDA-regulated products. To develop communications that are relevant, culturally appropriate, and meet the patients' and consumers' health literacy needs, FDA designs SBS research studies that provide an understanding of

patients' and consumers' beliefs, attitudes, feelings, and motivations related to various public health topics.

Examples
FDA implements a variety of social and behavioral science research approaches.

- Using patient and consumer interviews and surveys to determine how messaging, labeling statements, and claims related to a medicine's attributes, food consumption and cosmetic usage affect patients' and consumers' understanding and decision-making.

- Examining tobacco-related beliefs and perceptions held by subgroups (e.g., representing ethnically diverse populations) to improve our communication strategies and develop innovative public education campaigns aimed at preventing and reducing tobacco use across diverse populations (e.g., **The Real Cost Campaign**).

- Conducting extensive formative research, including more than 40 focus groups, representing the diverse backgrounds of consumers around the United States, to produce consumer-oriented educational materials for the ***Feed Your Mind* Initiative**. This agricultural biotechnology initiative provides consumers with science-based educational information informed by the latest science and research studies on the environmental, nutritional, food safety, economic, and humanitarian impacts of genetically engineered or bioengineered foods, commonly called genetically modified organisms.

- Using data from social media posts (e.g., Facebook and Twitter), and FDA archival data (e.g., FDA's Advisory Committee transcripts) to better understand patient and consumer perspectives for all FDA-regulated commodities.

- Evaluating different ways to assess the patient experience that complement existing survival and tumor information typically included in oncology clinical trials. FDA's **Project Patient Voice website** communicates and summarizes PRO data submitted in regulatory applications by some drug sponsors. As part of this effort, FDA is supporting research into analytic and visualization methods to communicate accurate and non-misleading symptom and functional data from clinical trials to aid in clinical decision-making for patients and providers.

RESEARCH CAPABILITIES, TOOLS, AND RESOURCES

Introduction

Research addressing each of the focus areas of regulatory science (FARS) is funded through a combination of FDA-funded mechanisms: intramural and extramural grants, and contracts managed by centers and Agency-wide offices. Agency resources are critical to fully support intramural and extramural research addressing the FARS. The **Office of the Chief Scientist (OCS)** facilitates coordination and administration of some of the shared resources in collaboration with centers and offices. OCS also oversees the Agency-wide Senior Science Council (SSC), comprising scientific leadership from each of the centers, and the Office of the Commissioner's component office. SSC provides advice and guidance to the Agency and center leadership on cross-cutting regulatory science issues, including on planning, reporting, programs, policies, and communication. FDA centers and offices have primary authority over their own research resources in terms of setting strategic priorities, allocating research resources to high-quality, mission-relevant scientific projects, and having in place systems for periodic and systematic evaluation of the research productivity, outcomes, and impacts.

Research Management and Collaborations

Centers and offices manage regulatory science research by evaluating it both prospectively and retrospectively, using internal and/or external scientific review. Many centers and offices also have research governance bodies to engage leadership in discussions of policies and decisions around research goals, priorities, and processes. Outcomes of such reviews are incorporated into decision-making, which informs resource allocation, such as funding, staffing, equipment, and laboratory space.

To identify best practices across the agency and better understanding of approaches used to evaluate the impact of research that is conducted or funded by FDA, the SSC-chartered the Research Impact Work Group.

FDA uses the **FDA Science Board** to perform periodic external reviews of the research programs conducted in centers and offices. These reviews are high-level and often focused on evaluation of the current portfolio, assessment of future trends, and needs for new research endeavors as well as providing input into the processes used to manage the research resources.

Researchers throughout the Agency comply with the **requirement to increase access to federally funded scientific research** by using data management plans to prospectively identify how and what types of research data underlying research published in peer-reviewed scientific journals may be shared, as appropriate. In addition, FDA's researchers are encouraged to publish their scientific findings in peer-reviewed scientific journals. In some rare cases (such as investigations of regulated products), the findings may not be published publicly, but the results are internally catalogued. All external research publications are collected in the publicly accessible **FDA-wide research publication database**.

Since FDA is a regulatory agency, the impact of its regulatory science research goes beyond just what FDA publishes in scientific journals. Often the expertise and results from our research directly informs development of voluntary consensus standards, regulatory policies, guidance documents, the **FDA Foods Program Compendium of Analytical Methods**, and review of regulatory submissions through guidance and regulatory decision-making on a daily basis.

FDA often partners with standard development organizations to identify and develop community consensus standards. The use of voluntary consensus standards can facilitate product development and reduce the amount of documentation needed in a regulatory submission, thus contributing to a more efficient

submission evaluation and, ultimately, improving time to market. Yearly, FDA participates in the development of The National Technology Transfer and Advancement Act (NTTAA) report. The Act mandates that all federal agencies use technical standards developed and adopted by voluntary consensus standards bodies, as opposed to using government-unique standards.

Technology Transfer and Public-Private Partnerships

Technology Transfer is the process of transferring skills, knowledge, technologies, and methods among governments and universities, as well as non-profit and industry organizations, to make sure that a wider range of users has access to scientific and technological innovations created by FDA scientists. These users can, in turn, develop and use the technology to create new products, processes, applications, materials or services. Legally required under the **Bayh-Dole Act (Patent and Trademark Law Amendments Act, Public Law 96-517)**, the **FDA Technology Transfer Program (FTTP)** provides services to support the effective transfer of FDA research results and FDA-created technologies to the market in support of public health. These services include evaluating employee invention reports to select the most effective mechanism for bringing the technology to the public, managing the patenting of new discoveries from FDA laboratories, and licensing of novel technologies, biological materials and animal models invented by FDA investigators. The FTTP also selects the appropriate technology transfer agreement type for collaborative research projects between FDA and other parties after carefully considering the goals of the investigators and their collaborator(s), project funding, the specifics of the exchange of materials and data, and the management of publications and intellectual property. Types of agreements include the Cooperative Research and Development Agreement, Research Collaboration Agreement, or Material Transfer Agreement. FDA also engages in scientific **Public-Private Partnerships (PPPs)** and consortia with other government academic, scientific, patient, and industry organizations to encourage the development of new tools to facilitate innovation in medical product development. An example of a PPP with FDA involvement is **The National Institute for Innovation in Manufacturing Pharmaceuticals**.

Physical Standards and Reference Materials

Physical standards and reference materials are substances or materials produced in a controlled environment

that are used as a "calibrator" to produce additional substances or materials (e.g., materials of documented purity certified by an analytical laboratory or other noncommercial establishment). FDA scientists may develop standards and reference materials and may depend on internal or external lab consortia for validation and distribution. In addition, external parties (e.g., **U.S. National Institute of Standards and Technology** and **National Institute of Biological Standards and Control** in the United Kingdom) develop standards and reference materials and depend on FDA laboratories to participate in validation studies. For example, annually, FDA develops, validates, and distributes the strain-matched standard of the seasonal and pandemic strains of the influenza vaccine for potency (effectiveness) testing. The Agency also participates in developing standards for a variety of regulated products that are often later adopted as international standards by the **World Health Organization** (WHO). Currently, FDA laboratories are involved in an international multi-laboratory study endorsed by WHO to validate reference materials for SARS-CoV-2 ribonucleic acid (RNA) and antibody detection assays. Some of FDA's laboratories also function as a **WHO Collaborating Center**.

Another example where FDA facilitates product development through references is the **FDA-ARGOS database** which provides *reference-grade microbial sequences* to enable sequence-based diagnostic assays.

Intramural Grant Programs

Centers and offices administer intramural research funding programs focused on a variety of topics and use different mechanisms, such as small competitive grant program.

In response to the growing number of cross-cutting science and technological issues arising from regulatory oversight of products in FDA's regulatory portfolio (i.e., see **FARS** for most current list of such regulatory science focus areas that have been identified by FDA), FDA developed a competitive grants program called the OCS Intramural Challenge Grants to foster opportunities for cross-center and office cooperation and collaboration and to serve as an incubator for innovative ideas.

FDA's Chief Scientist establishes highly innovative and high-risk projects that reflect FDA's overarching regulatory science focus areas including:

- Collaborative Opportunities for Research Excellence in Science champions FDA cross-center regulatory research nanotechnology efforts

- **Office of Minority Health and Health Equity** supports research on advancing minority health and health equity, understanding of health disparities, and projects that provide future directions for research that contributes to regulatory decision making.

- **Office of Women's Health Intramural Grants Program** aims to address gaps in current regulatory knowledge, set new directions in regulatory policies, or establish a new standard of excellence for research in women's health and sex and gender differences.

- **Medical Countermeasures Initiative** leads projects that address regulatory science gaps for countermeasures against chemical, biological, and radiological/nuclear threats and emerging infectious diseases.

- **Perinatal Health Center of Excellence Intramural Funding Program** applies research to understudied populations of the perinatal period (maternal, premature, neonatal and pediatric periods, as well as development throughout childhood).

Extramural Funding Mechanisms

To expand and complement FDA's intramural research capabilities and to spur innovation in the field of regulatory science in the extramural community, individual centers/offices as well as OCS, fund extramural research using various contract mechanisms and grants to address Agency regulatory science challenges. Depending on availability of appropriated funds, Centers and FDA may have grant and contract programs to support extramural research in very targeted areas.

OCS supports two FDA-level extramural funding mechanisms. One is a contract mechanism called FDA's **Advancing Regulatory Science Broad Agency Announcement** (BAA), which enables FDA to solicit ideas and approaches to facilitate the development and evaluation of FDA-regulated products from industry, academia, and other government agencies in areas where FDA has limited expertise or capacities through this specialized contract mechanism. In the future, the BAA will incorporate the FARS to communicate the Agency's most current regulatory science needs to solicit relevant proposals from the external scientific community.

FDA also collaborates with academic institutions to advance regulatory science through innovative research, training, and scientific exchange leveraging collaborative grants used to fund the **Centers of Excellence in Regulatory Science and Innovation Program (CERSI)**. Through the CERSI Program, FDA offers its scientific staff a range of opportunities, including research collaborations and access to regulatory science-related training, workshops, and seminars. These opportunities support FDA staff engagement while harnessing a broader community of scientific, technical, and medical expertise within the academic communities in areas of mutual interest in regulatory science. The CERSI Program also provides training opportunities for graduate students and post-graduate fellows to learn about regulatory science, thus creating more awareness in academic institutions about FDA's research and regulatory programs.

Scientific Education, Training, and Communication

Fellowship and Training Opportunities

FDA offers different types of internships, fellowships, and training opportunities to national and international students and postgraduate scientists as well as college and university faculty members. Centers also administer programs and targeted trainings to researchers and scientists at different career stages. For example, with the intent to educate the next generation of scientists, FDA hosts the Oak Ridge Institute for Science and Education (ORISE) Research Participation Program, which allows high school, college, and graduate students, recent graduates, post-doctoral scientists and university faculty to actively engage in research experiences with an FDA scientist who serves as a mentor. Another program, the **FDA-National Cancer Institute Inter-Agency Oncology Task Force Joint Fellowship Program** trains scientists in research and research-related regula-

tory review policies, and regulations to develop a skill set relevant to both the review and research areas. Additionally, FDA's **Service Fellowship** Program gives scientists the opportunity to accelerate and enhance their careers by working closely with leading authorities in FDA-related research while also learning about FDA regulatory review. FDA OMHHE also hosts a Genomic Science and Health Equity Post-Doctoral Fellowship in collaboration with the National Human Genome Research Institute at NIH.

Professional Development and Continuing Education

FDA provides resources and opportunities for research and review staff to remain current on key scientific advances, including providing training opportunities that translate knowledge from internal research programs to reviewers to inform regulatory review, policy, and regulatory decision-making, through a variety of internal seminar series.

Many scientific working groups also host educational workshops, seminars, or training activities to ensure FDA's scientific staff remain current on a variety of relevant topics to support review activities. For example, the FDA Genomics Working Group has an education subcommittee which provides educational opportunities in the use, analysis, and understanding of next generation sequencing for many years. Centers also have research-related governance committees, centers of excellence (e.g., immunology, oncology) and working groups that provide recommendations and guidance, research portfolio investments, and collaborate with the SSC and FDA scientific working groups.

With FDA's scientific and technical staff making up more than 65 percent of FDA's workforce across a multitude of disciplines, FDA provides staff with a wide range of professional development opportunities to stay current with the latest advances in science and technology. FDA staff have access to FDA's scientific professional development calendar on the Agency's intranet, which provides a comprehensive listing of relevant Agency-wide scientific professional development events sponsored by FDA and FDA partners (e.g., CERSI Program). In addition, researchers attend relevant trainings to stay compliant with regulatory and safety mandates.

Internally, FDA hosts lectures, workshops, poster sessions, and scientific experts from external organizations to share best practices and information. FDA also discusses emerging science topics in seminar series and journal clubs providing a forum for staff to stay current about scientific literature. Monthly, the FDA hosts the public educational series of the **FDA Grand Rounds**, presentations that highlight cutting-edge research underway across the Agency and its impact on protecting and advancing public health.

Additionally, the FDA hosts the biannual **FDA Science Forum**, which offers the public a first-hand look at how FDA's researchers use novel science and technologies to inform FDA's regulatory decision-making through roundtable discussions, poster sessions, and interactive presentations.

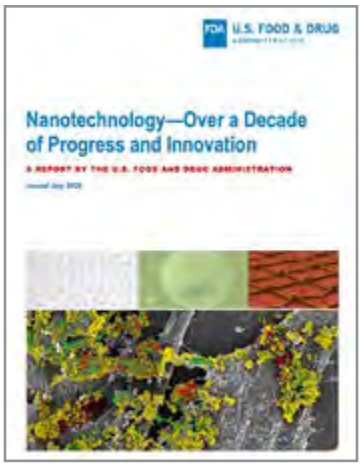
FDA also prioritizes continuing education for its staff and external stakeholders. FDA's **Continuing Education (CE) program** offers medical, pharmacy, and nursing CE credit for lectures, courses, and scientific rounds through the **CE Portal**. The **FDA Learning Portal** provides educational resources related to FDA's regulatory, product quality, safety responsibilities, and research for students, academia, and industry. FDA also provides **free online trainings** to state, local, and tribal regulatory partners.

Communication and External Meetings

OCS provides cross-agency scientific coordination (e.g., for emerging technologies, scientific issues involving multiple Agency components, standards coordination, and science communication) through the SSC and FDA scientific working groups. The SSC provides guidance to the Agency and center leadership on cross-cutting regulatory science issues, including planning, reporting, programs, policies, and communication. Chartered scientific working groups endorsed by the SSC and administered by the OCS serve FDA senior management as a scientific information resource, while also providing a forum for cross-center and office communication and fostering collaborations. The goals of the working groups include the following: communicate and share information among centers, when needed, or as feasible, coordinate scientific projects, and promote collaboration and exchange of resources and expertise. For example, the **Emerging Sciences Working Group** leverages scientific expertise and resources to conduct long-range horizon scanning to advise Agency and center leadership

on how emerging issues and cross-cutting scientific advances may affect FDA preparedness and trans-Agency activities.

FDA also engages with external partners across the globe to host public workshops, meetings, (including advisory committee meetings), and conferences covering a wide range of topics such as medical devices, tobacco products, vaccines, cell and gene therapy products, and combination products to share scientific expertise, research results, and develop future collaborations. For example, FDA released an updated **Nanotechnology Task Force Report** in advance of the annual **Global Summit on Regulatory Science (GSRS)** meeting in 2020. The GSRS is an international venue for discussion of innovative technologies and partnerships to enhance translation of basic science into regulatory applications within the global context.



FDA scientists and trainees stay up to date with the latest scientific knowledge and skills, while also sharing the results of their research by attending and presenting at relevant external scientific and professional society meetings, conferences, and courses.

Infrastructure

Facilities and Shared Resources

FDA's laboratory complexes house more than 2,500 researchers and analysts whose work contributes to the development of new approaches, standards, and methods for evaluating the safety, efficacy, quality, and performance of the diverse and complex products the Agency regulates.

These facilities include a variety of specialized facilities to support laboratory research, including vivaria, biosafety level (BSL)-3 laboratory suites, Animal Biosafety Level (ABSL)-2 and -3 procedure rooms, and an anechoic chamber.

FDA also provides a variety of core facilities—many of which are supported by the FDA Shared Resources Program for Regulatory Science. Centers share costs to allow researchers access to state-of-the-art technology, equipment, facilities, experts, resources and information. Examples of FDA's core facilities include the following: additive manufacturing of medical products (3D printing), microscopic imaging, flow cytometry, sequencing and other traditional biotechnologies, nanocore, electron microscopy, and advanced characterization technologies. Availability of core facilities to access expensive new technology provides FDA researchers a cost-effective way to stay current with the technologies

FDA regulates and advance research efforts.

FDA developed High Performance Computing (HPC) environments that provide FDA researchers the capability to perform computationally intensive processing, modeling, and analysis. The HPCs enable bioinformaticians and computational experts to tailor development of algorithms and pipelines in support of specific scientific investigations or regulatory review of submissions. Across the Agency, scientists and researchers look at data in ways not previously possible, such as data visualization tools to find patterns in large data sets, informing the determination of risks and benefits with computational modeling and simulation and analysis of next generation sequencing methods to address scientific questions related to regulated products (such as detection and identification of the source of food-borne outbreaks).

In addition, the FDA Biosciences Library provides access to electronic journals, eBooks, over 50 online databases and research services such as assisting with systematic reviews and search strategies, available to staff at all FDA locations.

Safety and Compliance

FDA prioritizes the safety of all staff, as well as compliance with applicable laws and regulations including, but not limited to laboratory safety, use of animals, the environment, human subjects, and select agents and toxins. To ensure compliance with safety and other regulatory requirements, staff complete trainings on a regular basis relevant to their work duties or potential exposure to workplace hazards.

In addition, FDA promotes laboratory quality and adherence to quality elements among FDA researchers and regulatory personnel to achieve robust and reproducible findings. FDA researchers are encouraged to publish original research findings in scientifically accepted, peer-reviewed scientific journals after appropriate review and clearance. Quality programs are imperative to ensure the highest scientific rigor that leads to data-based decisions.

The **Office of Laboratory Safety (OLS)** partners with center and office staff to implement robust workplace health and safety programs and provide guidance to FDA laboratorians on laboratory quality management and environmental protection. OLS strives to support the Centers and Offices in identifying, quantifying, and controlling workplace hazards inherent to accomplishing the mission of FDA. Compliance with the **National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)** as well as use of hazardous biological agents and toxins is overseen by OLS through FDA's Institutional Biosafety Committee. Likewise, compliance with the United States Nuclear Regulatory Commission requirements for working with radioactive materials is overseen by OLS

through FDA's Radiation Safety Program.

OLS works in conjunction with Employee Safety and Occupational Health (ESOH) Staff, who oversee occupational health services, ergonomics, and Automated Emergency Defibrillator (AED) programs. At most FDA properties, FDA employees oversee facilities maintenance and engineering activities and conduct preventive maintenance and annual inspections of building equipment and systems. The activities among these groups are interwoven to support safe research and the attainment of regulatory goals.

FDA researchers follow and uphold principles of scientific integrity to promote an environment of robust scientific debate where integrity of information is ensured, all views are considered, and scientific decisions are protected from political influence. This protects FDA's ability to reach sound decisions and to retain the public's trust. The **Office of Scientific Integrity** works to ensure that FDA's policies and procedures are current and applied across the Agency; resolves scientific disputes that may arise internally or externally and that are not resolved at the Agency's center levels; and advise the Chief Scientist and other senior FDA leaders on appropriate responses. FDA provides author services and resources to FDA researchers to ensure that they are submitting articles to reputable journals with rigorous peer review instead of predatory publishers.

FDA researchers may occasionally conduct research involving human subjects. FDA's Institutional Review Board is generally responsible for overseeing the protection of human subjects in FDA-conducted research, consistent with applicable HHS and FDA regulations, such as the HHS Policy for Protection of Human Subjects (45 CFR part 46), Protection of Human Subjects (**21 CFR part 5021 CFR part 50**) and Institutional Review Boards (**21 CFR part 5621 CFR part 56**).

While FDA strives to reduce the use of animal tests, animal tests still are often needed to support development of FDA-regulated products. FDA has three (3) animal programs to support the FDA mission, each with its own **American Association for Accreditation of Laboratory Animal Care** accreditation, Attending Veterinarian, Institutional Official, and **Institutional Animal Care and Use Committee**. In addition, each of FDA's animal programs follow the policies of the **National Institutes of Health Office of Laboratory Animal Welfare** and obtain assurances to demonstrate their compliance. OCS provides general guidance and develops Agency-wide policies supporting the safe care and use of animals through the Animal Welfare Council.

ACRONYMS

*FDA centers and offices represented on the FARS Agency-wide Committee

3 Rs	Replace, reduce, and refine [the use of animals in research]
3D	Three dimensional
AAV	Adeno-associated virus
ABSL	Animal Biosafety Level
AE	Adverse event
AED	Automated Emergency Defibrillator
AI	Artificial intelligence
AMR	Antimicrobial resistance
ANDA	Abbreviated new drug application
BAA	Advancing Regulatory Science Broad Agency Announcement (FDA)
Bayh-Dole Act	Patent and Trademark Law Amendments Act, Public Law 96-517
BEST	Biologics, Effectiveness and Safety system (FDA)
BSL	Biosafety Level
C. botulinum	Clostridium botulinum
C. diff.	Clostridioides difficile
CAD	computer-aided diagnostic
CAERS	Center for Food Safety and Applied Nutrition Adverse Event Reporting System (FDA)
CAR T-cell therapies	chimeric antigen receptor T-cell therapies
CARB	Combating antibiotic-resistant bacteria
CBD	Cannabidiol
CBER*	Center for Biologics Evaluation and Research (FDA)
CBRN	Chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention (U.S.)
CDER*	Center for Drug Evaluation and Research (FDA)
CDRH*	Center for Devices and Radiological Health (FDA)
CE	Continuing Education
CERSIs or CERSI Program	Centers of Excellence in Regulatory Science and Innovation program (FDA)
CFR	Code of Federal Regulations (U.S.)
CFSAN*	Center for Food Safety and Applied Nutrition (FDA)
CID Program	CID Pilot Meeting Program (FDA)
CIDs	Complex innovation trial design
CM	continuous manufacturing paradigms
COA	Clinical outcome assessment
COVID-19	Coronavirus Disease 2019
CTP*	Center for Tobacco Products (FDA)
Cures Act	21st Century Cures Act, Public Law 114-225
CVM*	Center for Veterinary Medicine (FDA)
DHCoE	Digital Health Center of Excellence

DHT	Digital health technology
DoD	U.S. Department of Defense
DQSA	Drug Quality and Security Act, Public Law 113-54
E. coli	Escherichia coli
ECG	Electrocardiogram
EHR	Electronic health record
ESOH	Employee Safety and Occupational Health (staff)
EVD	Ebola Virus Disease
FAERS	FDA Adverse Event Reporting System (FDA)
FARS	Focus Areas of Regulatory Science
FD&C Act	Federal Food, Drug, and Cosmetic Act, Public Law 97-414
FDA	Food and Drug Administration (U.S.)
FDA ARGOS	FDA Database for Reference Grade Microbial Sequences
FMT	fecal microbiota for transplantation
FTTP	FDA Technology Transfer Program
GMO	Genetically modified organism
GSHE	Genomic Science and Health Equity (GSHE Postdoctoral Fellow)
GSRS	Global Summit on Regulatory Science
HHS	Department of Health and Human Services (U.S.)
HPC	High performance computing
HT	Hormone therapy
HUD	Humanitarian Use Device (HUD) program
IAA	Inter-Agency Agreements
ICH	International Conference for Harmonisation
LFFM	flexible lab funding model
Lupus	systemic lupus erythematosus
MAUDE	Manufacturer and User Facility Device Experience Database (FDA)
MCM	medical countermeasure
MedDRA	Medical Dictionary for Regulatory Activities
MIC	mean inhibitory concentration
MIDD	Model-informed drug development
MIPD	Model-informed product development
ML	Machine learning
MVD	Marburg Virus Disease
NARMS	National Antimicrobial Resistance Monitoring System for Enteric Bacteria
NASEM	National Academies of Science, Engineering & Medicine
NCATS	National Center for Advancing Translational Sciences
NCTR*	National Center for Toxicological Research (FDA)
NDMA	carcinogen; N-Nitrosodimethylamine, also known as dimethylnitrosamine
NEST(cc)	National Evaluation System for health technology (coordinating center)
NGS	Next generation sequencing
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health (U.S.)
NIH Guidelines	NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NTI	Narrow therapeutic index

NTTAA	National Technology Transfer and Advancement Act
o2S2PARC	Open Online Simulations for Stimulating Peripheral Activity to Relieve Conditions
OCE*	Oncology Center of Excellence
OCE*	Oncology Center of Excellence (FDA)
OCS*	Office of the Chief Scientist (FDA)
ODA	U.S. Orphan Drug Act, Public Law 97-414
OLS	Office of Laboratory Safety (FDA)
OMHHE*	Office of Minority Health and Health Equity (FDA)
OO*	Office of Operations (FDA)
OOPD*	Office of Orphan Products Development
OPCTG	Program Orphan Products Clinical Trials Grants Program (FDA)
OPT*	Office of Pediatric Therapeutics
ORA*	Office of Regulatory Affairs (FDA)
OWH*	Office of Women's Health (FDA)
PBPK	Physiologically-based pharmacokinetic
PD-1	Programmed cell death protein 1
PDC	Pediatric Device Consortia (PDC) Grants Program
PDUFA VI	Prescription Drug User Fee Act VI included as part of FDA Reauthorization Act of 2017, Public Law 115-52
PFAS	Per- and polyfluoroalkyl substances
PPI	Patient preference information
PPP	Public-private partnership
PRO	Patient-reported outcome
radiation sickness	acute radiation syndrome
RCA	Research Collaboration Agreements
RCT-DUPLICATE	Randomized Controlled Trials Duplicated using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology
RNA	ribonucleic acid
RPD	Rare Pediatric Disease (RPD); referencing the Priority Review Voucher Program
RWD	Real-world data
RWE	Real-world evidence
RWE	Real-World Evidence
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBS	Social and behavioral science
Sentinel	Sentinel System (FDA)
SHIELD	Systemic Harmonization and Interoperability Enhancement for Lab Data
SRP	Safety Reporting Portal
SSC	Senior Science Council (FDA)
The Agency	Food and Drug Administration (U.S.)
The Virtual Family	A set of anatomically correct whole-body computational models based on multimodal imaging
U.S.	United States of America
UMaryland	University of Maryland
UMaryland-CERSI	University of Maryland Center of Excellence in Regulatory Science and Innovation
USDA	US Department of Agriculture
VAERS	Vaccine Adverse Events Reporting System (FDA)
VCPR	Veterinary client patient relationship

Vet-LIRN	Veterinary Laboratory Investigation and Response Network
VICTRE	Virtual Imaging Clinical Trials for Regulatory Evaluation
WGS	Whole genome sequencing
WHO	World Health Organization
zoonotic disease	diseases that can spread from animals to people

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Food and Drug Administration

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