



ADMINISTRATION

2021

Advancing Regulatory Science at FDA:

FOCUS AREAS OF REGULATORY SCIENCE (FARS)



OPENING STATEMENT FROM THE COMMISSIONER



Commissioner Stephen Hahn, MD

At FDA, regulatory science research plays a critical role in supporting the science-based decision-making we do every day to protect, promote, and advance public health by ensuring the safety and efficacy of medical products, as well as the safety of the nation's food supply. FDA advances regulatory science by developing the tools and methods, and obtaining the data needed to speed innovation, improve regulatory evaluation, and facilitate availability of FDA-regulated products that address unmet medical and public health needs. This research enables safe and effective human and veterinary medical products to be brought to market to support these unmet public health needs, informs how we educate our youth about the dangers of tobacco use, and protects the safety of our food.

As new science and technology translate into innovative products or may be useful to improve evaluation of existing products, FDA engages the intramural and extramural scientific communities to protect, promote, and advance public health. FDA invests in regulatory science research to address gaps in scientific understanding or to develop tools and methods needed to inform regulatory decisions and policy development. For example, to support decision-making, FDA scientists are harnessing wider and wider networks of electronic healthcare records to enable near real-time postmarket surveillance and using real-world data to augment clinical trial data. In addition, FDA is implementing next-generation sequencing-based methods to monitor for development of novel antimicrobial resistance and to detect and trace outbreaks of food-borne illnesses. FDA's scientific efforts are also shepherding the development of innovative medical products and advancing development of technologies to replace, reduce, refine (the 3 Rs) dependence on animal studies through studies of new, fit-for-purpose non-clinical tools, standards, and approaches that improve predictability.

While the scientific progress of FDA is enabling the entry of innovative products into the marketplace to improve the lives of the American public, FDA needs to continue to keep pace with evolving science and technology. The *Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS)* report was developed to reflect important changes to the science and technology underpinning FDA-regulated products. The FARS report is intended to identify and communicate priority areas where new or enhanced investments in regulatory science research capacity are essential to support FDA's regulatory and public health mission. Increased attention from the research community to the regulatory science topics identified as FARS will aid the development of innovative products, provide data to inform regulatory decision-making, and improve guidance to sponsors.

The FARS are organized across the three strategic initiatives that I shared at the beginning of 2020: **Unleashing the Power of Data; Increasing Choice and Competition through Innovation; and Empowering Patients and Consumers**. In addition, the FARS includes *Public Health Emergency Preparedness and Response*, given that FDA plays a critical role in supporting response efforts to the Coronavirus Disease 2019 (COVID-19) pandemic.

The research conducted to support the FARS as well as center- and office-specific research comprises FDA's robust research portfolio. As science and technology continue to rapidly evolve, FDA has positioned itself to keep pace and adapt, ensuring that it remains at the forefront of the regulatory science research that supports its regulatory mission.

These four strategic initiatives support FDA's mission to protect, promote, and advance public health. To do this, it is paramount that we leverage our collective regulatory science expertise and work together to improve the lives of patients and consumers. I am honored to work among FDA's talented and innovative scientists and pleased to share our focus areas of regulatory science.

OPENING STATEMENT FROM THE CHIEF SCIENTIST



Chief Scientist RADM Denise Hinton

As FDA's Chief Scientist, I am proud of the comprehensive and often groundbreaking research our scientists conduct to protect, promote, and advance public health. Every day, FDA research scientists address regulatory challenges to provide scientific and objective data, tools, and expertise to support evaluation of FDA-regulated products.

At FDA, we are committed to delivering outcomes using sound science and data. We do this by performing intramural research and scientific activities, and by collaborating with stakeholders in the scientific community to ensure that we have the expertise and resources to improve processes, inform decision-making, and enable innovation in support of FDA's mission.

One of the purposes of the Focus Areas of Regulatory Science is to communicate the importance and impact of FDA's cross-cutting scientific research and activities. To stay ahead of evolving regulatory needs, the FARS are designed to be agile to permit regular updating to ensure the FARS include the most current topics for FDA's research to address to fulfill our regulatory responsibilities.

As we face the challenges and opportunities of 21st century regulatory science, my Office remains dedicated to continuing its support of FDA centers and offices as we work together and with the broader scientific community to harness the vast potential of new science and rapidly evolving technologies in support of FDA's mission.

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INTRODUCTION





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, and tobacco, to medical products, such as drugs, biologics, and devices. Together, FDA's multi-disciplinary workforce of **approximately 18,000 employees** supports the oversight of FDA-regulated products. FDA is responsible for the oversight of more than **\$2.8 trillion** of food, medical products, and tobacco where FDA's regulated portfolio accounts for **about 20 cents of every dollar** spent by consumers in the United States.

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**

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.

Law 97-414), and other laws, to fulfill its **public health mission**. FDA scientists conduct **regulatory science** research 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 develop-

ment. While industry focuses on product development and academia focuses on the scientific underpinnings, FDA concentrates on developing test methods, models and knowledge of the science needed to support regulatory evaluation. Regulatory science research is essential because it enables FDA to understand and assess risk, prepare for and respond to public health emergencies, and ultimately help ensure the safety or reduce the harm of products used or consumed by patients and consumers by providing scientific, non-biased, and objective expertise. FDA's regulatory science research results in a variety of outcomes, including the development of assays, animal models, data analysis tools, and reference material or standards used by FDA and sponsors developing FDA-regulated products. Data arising from regulatory science research supports education and sharing identified best practices through guidance with national and international peers, through regulatory decision-making, development of scientifically sound guidance documents, review and marketing authorization decisions, regulations, consumer advisories, labeling, industry warnings, and recalls.

Approach

In 2011, FDA developed a **strategic plan for regulatory science** that identified eight priority areas where new or enhanced engagement in regulatory science research was essential to advancing its regulatory mission. In 2013, a **ninth priority area** was added. In 2020, recognizing that the science and technology underpinning FDA-regulated products evolved significantly since 2011, FDA formed an Agency-wide committee to develop an efficient way to communicate its regulatory science activities. The committee developed the report **Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science** (FARS) to identify and communicate areas FDA has identified as needing continued targeted investment in regulatory science research to fulfill FDA's regulatory and **public health mission**. The format is designed to be easy to update to accommodate frequent updates and revisions to align with the rapid pace of scientific advancement as well as evolving priorities and research activities. Each FARS follows the same format—a description of why the focus area is important to FDA and examples of recent and ongoing research.

The FARS are not intended to be a comprehensive list of all FDA research needs, but rather generally identified research that affects more than one FDA center or office. FDA recognizes that many additional areas exist of ongoing regulatory science research. Center- and office-specific research outside of the current FARS are of no less importance than the identified FARS.

The FARS are organized across **strategic initiatives identified by Commissioner Hahn in 2020**. The committee tasked with developing the FARS added the initiative Public Health Emergency Preparedness and Response given FDA research's critical role in supporting this theme. Therefore, the FARS are organized across each of four initiatives:

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

FARS-related research will be conducted through intramural and extramural research programs identified by FDA centers and offices. **Research Capabilities, Tools, and Resources** highlight available FDA resources, capabilities, and tools that centers and offices will leverage when performing research in the focus areas. They are organized into the following sections:

- **Research Management and Collaborations**
- **Scientific Education, Training, and Communications**
- **Infrastructure**

Cross-cutting Topics

In developing the FARS, FDA determined that certain topics did not lend themselves to be a stand-alone FARS due to their broad application. As such, FDA identified the following cross-cutting topics underlying much of FDA's regulatory science research: **Lifecycle of FDA-Regulated Products**, **Women's Health Research**, **Minority Health and Health Equity Research**, and the **One Health Initiative**.

The **Coronavirus Disease 2019 (COVID-19)** pandemic is another cross-cutting topic reflected in many of the research examples listed in the FARS. COVID-19 is a contagious respiratory illness caused by infection with a novel strain of the coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This is notable because in 2020, FDA mobilized a **rapid response** to the pandemic including conducting regulatory evaluations of medical products used to diagnose, treat, or prevent COVID-19, and developing new research programs to facilitate development and regulatory evaluation of these critical **medical countermeasures**. For example, FDA scientists developed a **SARS-CoV-2 reference panel**. This reference panel provides a tool for developers of COVID-19 diagnostic assays to perform an independent performance validation step for diagnostic tests of SARS-CoV-2 infection that are used for clinical, not research, purposes. The FDA panel is available to commercial and laboratory developers who interact with FDA through the **pre-emergency use authorization process**.

Lifecycle of FDA-Regulated Products

As part of its regulatory responsibilities, FDA regulates one or more aspects of a product's 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, such as chimeric antigen receptor T-cell therapies (CAR T-cell therapies), 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

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 Generic Alternatives for Complex Drugs	✓	✓	✓	✓
	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				✓

licensure, approval, or clearance of an FDA-regulated medical product. Therefore, a combination 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-regulated products. To fulfill this commitment, FDA aims to improve the data sources and analytical approaches to support postmarket activities. View how the FARS apply to the product lifecycle in the table on page 10.

Women's Health 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) funds research and development activities related to advancing the science of women's health and sex and gender differences. OWH focuses funding on cross-cutting research with FDA centers to expand existing research projects and foster new collaborations. OWH works with other governmental agencies, academia, women's research organizations, and other stakeholders

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.

to facilitate research projects and scientific forums to advance FDA's understanding of women's health and sex and gender differences' impact 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. In addition, OWH provides extramural funding through the **Advancing Regulatory Science Broad Agency Announcement (BAA)** and **Centers of Excellence in Regulatory Science and Innovation (CERSIs)** 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. Results from OWH-supported research have led to safety labeling changes, product development guidance for industry, and new evidence-based communications about FDA-regulated products used by pregnant women. [Learn more about women's health research.](#)

Minority Health and Health Equity Research

FDA's Office of Minority Health and Health Equity (OMHHE) was established in 2010 to provide leadership and policy direction on minority health, health disparity, and health equity matters for FDA. OMHHE works with FDA centers, offices, and public- and private-sector stakeholders, including, academia, government agencies, and non-profit organizations to advance health equity-focused research, education, and scientific exchange.

OMHHE leverages various funding mechanisms, collaborations, and partnerships to achieve its mission. The OMHHE Challenge Grants support intramural research and the BAA and CERSI programs and interagency agreements support extramural research. OMHHE's efforts enable innovative research to answer pressing health disparity and regulatory science research questions to deliver valuable public health information to diverse communities and to aid in shaping regulatory decisions.

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. OMHHE 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.

OMHHE research projects contribute to assessing the safety and efficacy of FDA-regulated therapeutic products among diverse populations, and focus on areas such as product labeling, precision medicine, multiple myeloma, clinical trial diversity, Sickle Cell disease, Alzheimer's disease, systemic lupus erythematosus (lupus), and triple-negative breast cancer. For example, social listening tools helped support OMHHE's portfolio of knowledge and promoted health and safety communication to strengthen patient and consumer decision-making on FDA-regulated products. In addition, OMHHE's breadth of work is reflected across the Agency through published guidances such as [Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies](#) and [Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs](#). Learn more about [minority health and health equity research](#).

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 the three One Health domains of human health, animal health, and 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 disease (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, 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 surveils 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.



FOCUS AREAS OF REGULATORY SCIENCE

Public Health Preparedness and Response





Introduction

FDA undertakes preparations 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 promote public health to prevent a public health emergency, and, when one occurs, during a public health emergency.

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 also expedites approval of generics to help alleviate drug shortage of certain products as needed.

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 **Labora-**

tory Flexible Funding Model to increase chemical, radiological and microbiological resources for domestic partners to respond to public health events. Resources include training, coordination, and data sharing to create a food shield.

Medical Countermeasures and Preparedness for Emerging Infectious Diseases

Importance to FDA

Medical countermeasures, or MCMs, are FDA-regulated products (biologics, drugs, devices) that may be used to diagnose, prevent, protect from, 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 and emerging infectious diseases preparedness. 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).
- 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 toxic chemicals in food substrates, such as *C. botulinum*, ricin, and abrin.
- Evaluating the quality of the immune response, including cross-reactive protection of potential universal influenza vaccines.
- 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.

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 (sterilized in their final holding container) since some are composed of biological materials that may lose their ability to work as intended when sterilized. Examples of biological materials include human blood and blood components, therapeutic proteins, monoclonal antibodies, live virus vaccines, certain gene therapy vectors, and cell-based therapies.

To address these issues, FDA encourages 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, terminally sterilizing drugs, removing or inactivating methods applied to traditional biotechnology products); or
- Detection (e.g., screening of the blood supply to remove units carrying human pathogens).

Example

- 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 continue 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.

Substance Use Disorders

Importance to FDA

Substance use disorder is the persistent use of substances with abuse potential such as opioids, stimulants, cannabis, or nicotine-containing tobacco products, despite substantial harm and adverse consequences. In the United States, opioid use-related death is a recognized public health emergency. Furthermore, using multiple prescription medications and illicit products (polysubstance use) has been associated with increased incidence of substance use disorder and drug-related deaths.

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 the treatment of opioid use disorder (**containing buprenorphine, methadone, or naltrexone as active ingredients**), 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. FDA is also concerned with the negative health effects associated with tobacco product use, and reviews, among other things, the toxicity and potential abuse liability of new tobacco products before they can be introduced to interstate commerce.

Examples

FDA supports or performs research to address substance use disorders:

- Developing models to evaluate respiratory risk associated with the simultaneous use of opioids and other sedative psychotropic drugs and mechanistic-based computational models to predict required naloxone reversal doses for novel opioids.
- Evaluating infants receiving opioid replacement drug therapy for opioid withdrawal syndrome for 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 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 the microorganism resistant to antimicrobial products (e.g., antibacterial, antiviral, or antifungal drugs). Antimicrobial products used to treat and cure an infection 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 tackling 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 earlier, monitor it, and minimize resistance development. FDA also works to improve these approaches to better understand how AMR appears and spreads. In addition, FDA facilitates the development of new drugs and biologics to prevent or fight 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 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.

- The FDA-led **National Antimicrobial Resistance Monitoring System for Enteric Bacteria** public health surveillance system implements enhanced tools to conduct surveillance of antimicrobial use and resistance data to better track resistance trends and outbreaks in foodborne and other enteric (intestinal) bacteria. These methods include whole genome sequencing for all isolates collected and global data sharing to expand the public databases tracking AMR at the **National Center for Biotechnology Information AMRFinderPlus** and **FDA's Salmonella Resistome Tracker**.
- 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, Pew Charitable Trusts, academia) to better understand clinical management practices and health outcomes.
- Other 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.
- Effective preventive vaccines indirectly decrease the need for antimicrobial use. FDA performs studies and develops models to facilitate the development of safe and effective vaccines against pathogens like *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, and *Clostridioides difficile*. 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 that may occur when bacterial cultures are treated with single antibiotics. Using a hollow fiber system, FDA has demonstrated that combinations of three antimicrobials can 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 will bolster clinical approaches to reduce 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 including imports and exports and human dietary supplements and excluding meat, poultry, fish, 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, deployment of those methods to domestic and global partners, and analysis of data from various sources. FDA prioritizes communicating results and activities related to the food supply to ensure the safety of the public and their animals.

Examples

FDA research supports food safety by:

- Using whole genome sequencing (WGS) to help investigate pathogen contamination of human foods and contamination of animal food that may have been potentially exposed and shared with humans. WGS is used to: characterize selected pathogens, provide linkages to human clinical illnesses identify genes that might not be found with routine testing, and 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 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 and more sensitive testing methods to measure low levels of PFAS concentrations in food. The analytical method developed can be used to test specific groups of food, as well as to focus efforts on foods grown or produced in areas associated with environmental PFAS contamination.

- Investigating the relationship 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 ways to detect food contaminants and markers of unapproved product irradiation in animal diagnostic samples from animals that consume pet food, 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.
- 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.

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 a risk to patients. 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 infection and over 60 deaths in 20 states, leading to enactment of the [Drug Quality and Security Act \(DQSA, Public Law 113-54\)](#). The DQSA established a new, voluntary category of compounders (outsourcing facilities), which are inspected by FDA. 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 engaged with the National Academies of Science, Engineering & Medicine (NASEM) to [conduct research on the safety and effectiveness of multi-ingredient compounded topical pain creams](#). NASEM provided FDA with its analysis on May 13, 2020, which concluded, among other things, that there is limited evidence to support the use of compounded topical pain creams in the general adult population, and that there is inade-

quate data to support conclusions about the safety of ingredients in these products. FDA is reviewing the reports and considering next steps. These data will generally help inform the public and Agency decision-making.

- FDA also engaged NASEM to **assess treating patients with compounded hormone therapy (HT) products and the availability of scientific evidence for their safety and efficacy**. Unapproved compounded HT products, such as progesterone and testosterone, are sometimes used instead of FDA-approved drug products for hormone replacement therapy. Some compounders market Compounded HT products as superior to FDA-approved drugs by saying they are *more natural, safer, or better* for patients. NASEM released a report on July 1, 2020, stating that there was a lack of rigorous evidence of safety and effectiveness from well-designed or properly controlled clinical studies. NASEM noted the lack of high-quality clinical evidence and minimal oversight of compounded HT products raises a public health concern. FDA is currently reviewing the NASEM report and considering next steps. These data will generally help inform the public and Agency decision-making.
- In collaboration with the University of Maryland Center of Excellence in Regulatory Science and Innovation (UMaryland-CERSI), FDA is **engaged in a three-year effort to examine the clinical use of drugs compounded from certain bulk drug substances**. UMaryland-CERSI will conduct interviews, focus groups and surveys with health professionals to better understand how compounded drugs that contain these substances are used in patient care. Information obtained by this research will help inform FDA's work to develop lists of bulk drug substances that may be used in compounding as described in sections 503A and 503B of the **Federal Food, Drug, and Cosmetic Act (FD&C Act, Public Law 97-414)**, and generally help inform the public and Agency decision-making.

- In collaboration with the **Johns Hopkins University CERSI**, FDA initiated **research to evaluate available evidence on the safety and effectiveness of each of six bulk drug substances** (inositol, methylcobalamin, glutathione, 2,3-dimercapto-1-propanesulfonic acid sodium, oxytocin, and melatonin) used in compounded drugs for patients with autism spectrum disorder. The research includes examination of how compounded drug products containing these ingredients are used in clinical practice.

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

Individualized therapeutics is the development of therapeutics for 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 *ultrarare* 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, 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., differences in peoples' genes, environments, and lifestyles). The goal of precision medicine is to match the right treatments to the right patients 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 (omics) to advance major breakthroughs in thinking about diagnosis, prognosis, and treatment of disease. The FDA created **precisionFDA**, a cloud-based community research and development portal that engages users across the world to share data and tools to test, pilot, and validate existing and new bioinformatics approaches to NGS processing. Pharmacogenetics studies how individuals respond differently to drug therapies based on their genetic make-up or genes 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 the development of mechanistically targeted therapeutics.

Examples

- Bacteriophage (phage) therapy (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 resistance of the bacteria to 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 show promise for treating several types of rare genetic diseases, and lentiviral vectors have been found to be effective at delivering genes to the hematopoietic system. In addition to gene therapies, 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 reproducibly and safely. 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 understand the potential for unintended changes to the genome that may have negative consequences.
- Rare diseases, as generally defined in the **U.S. Orphan Drug Act (Public Law 97-414)**, are diseases or conditions with a prevalence of fewer than 200,000 persons in the United States. About 30 million Americans are affected by 7,000 known rare diseases, but only a few hundred of these rare diseases have approved treatments. The **Orphan Products Clinical Trials Grants Program** (OPCTG Program) is an incentive program that supports clinical trial research of products including drugs, biologics, medical devices, and medical foods for use in rare diseases and conditions where no current therapy exists or where the proposed product will be superior to the existing therapy. The OPCTG Program provides grants for clinical studies on safety and/or effectiveness that will either result in, or substantially contribute to, market approval of these products. Since 1983, clinical trials under this program have facilitated the marketing approval of 70 products.
- 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 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 Act VI**, which was enacted as part of the **Food and Drug Administration 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 optimal 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/or effectiveness of the population intended to use the drug, 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 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 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.*), 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.

- Developing tools to determine how gut microbiota composition and functionality changes in response to specific dietary changes. Once developed, these tools may be useful to analyze the impact on the microbiome from consumption of any food, dietary supplement or food ingredient (e.g., high-intensity sweeteners).
- 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 **foods made from cultured cells** of animals. While such efforts show a feasible means of food production from both technical and economic perspectives and will increase the variety of options, it would be helpful for FDA to have detailed compositional data for a variety of nutritive and non-nutritive

constituents from a wide range of conventionally-sourced animal tissues to inform assessments of both identity and safety regarding products of this technology. 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.

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 United States 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. The following examples address 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 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.
- 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.

Increasing Access to Generic Alternatives for Complex Drugs

Importance to FDA

FDA supports the development of generic versions of complex drug products because they represent nearly one-third of drug products currently used but have less generic competition than non-complex drugs. The presence of generic drugs on the market helps to ensure availability of quality medicines at a lower cost to the American public.

FDA prioritizes research to develop methods and approaches for establishing the bioequivalence of generic versions of complex drugs. Data on bioequivalence informs FDA's review of applications and development of **guidance documents for industry** addressed to generic drug developers. Some factors considered when determining whether drugs are complex include molecule size, and mixtures of active or inactive components or formulations. 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.

Examples

FDA researchers apply quantitative methods and modeling approaches to evaluate generic drugs such as the development of physiologically-based pharmacokinetic (PBPK) models for locally acting drugs and quantitative clinical pharmacology models.

- Using 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 clinical endpoints when needed. NTI drugs have small differences in dose or blood concentration, which 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 product. 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.

Product Development Tools

Publicly available FDA-endorsed **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 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. Several reasons are listed below.

- Identification of a biomarker 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 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 find out if 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** process 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. Under the **21st Century Cures Act (Public Law 114-225)**, **biomarker qualification** involves a three-stage submission process to develop a biomarker for regulatory use.

The **Biomarkers, Endpoints, and other Tools** resource is a living document developed jointly by FDA and 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**.

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

Importance to FDA

Animal studies are traditionally used to assess the risk, safety, efficacy, 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 predictivity. 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 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 will provide FDA data to inform decisions about clinical investigations, licensures, and other products such as food, cosmetics, and tobacco.

The development and eventual availability of **new alternative methods** that more accurately identify, predict, evaluate and reduce the degree and likelihood of risks will likely provide enhanced prediction of the risk and/or safety outcomes. 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, and 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.
- Emerging technologies such as in vitro microphysiological systems, have the potential to produce predictive data supporting development of human and veterinary products. FDA is looking to develop performance criteria in order to provide a realistic assessment of the potential of these new tools for safety and efficacy testing.
- 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.

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**, included as part of the **Food and Drug Administration Reauthorization Act of 2017 (Public Law 115-52)**.

MIDD applications include 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 mechanism, product performance optimization, and informing policy.

FDA has committed significant 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 with the following approaches.

- 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.

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- Making available **The Virtual Family**: a set of anatomically correct whole-body computational models based on multimodal imaging.
 - **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. Research is ongoing to 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** on a potential nicotine public health standard on the prevalence of tobacco use, tobacco-related mortality, and life-years gained.



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 machine learning (ML) and [artificial intelligence \(AI\)](#). FDA is working to obtain more and higher-quality data, be more proactive in gathering data, and be more creative and thorough in analysis and interpretation.

The healthcare setting produces abundant, multifaceted health data amassed from numerous observational, clinical, and experimental sources. These health data include but are not limited to data from electronic health records (EHRs), medical imaging, genomic sequencing, payor records, pharmaceutical research, digital health technologies (DHTs), and medical devices.

The breadth, depth, and diversity of big 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 data interpretation may give rise to conflicting conclusions.

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 big data can help fill knowledge gaps and better inform FDA regulatory decision-making. FDA

is interested in developing new approaches to harnessing this power 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 clinical trial 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 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 additional 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, biologics, 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 postmarketing 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**
- 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** contains reports of adverse events involving medical devices.

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.
- Leading several studies, as part of Sentinel, in response to the COVID-19 pandemic. Literature suggests 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.

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 therapeutic development, regulatory assessment, and postmarket surveillance, to name a few among many other potential applications of AI. 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 methodologies using machine learning (ML). 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 and ML, new regulatory questions introduced by using AI applications, and the impact of AI solutions across the lifecycle of FDA-regulated products.

Examples

FDA advances understanding and use of AI to support a diverse set of needs FDA-related to regulated products using several approaches:

- Exploring the use of ML algorithms to:
 - Target high-risk seafood products offered for import;
 - Detect adverse events in different data sets, including postmarket data; and
 - Study the effects of synthesized data sets for training and testing in both pre-market testing and the FDA-regulated product lifecycle.
 - 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.
- Using natural language processing and human workflows to identify how to code adverse events (AE) in the **International Conference for Harmonisation Medical Dictionary for Regulatory Activities (MedDRA)**. This information is used in drug labels or package inserts to support postmarket safety surveillance. The evaluation compares human-only versus automated support of drug label development activities. FDA collects and evaluates data on the efficiency of using automated support to determine the status of MedDRA-coded AE-labels.
- 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. Assessing the complexity upon receipt enables FDA to allocate the correct amount of resources early in the review cycle.
- Studying how AI can combine diverse data so clinical trial results can be analyzed in a more comprehensive and expeditious way.
- Developing and applying ML algorithms and natural language processing to retrieve and synthesize drug-related AE information from FDA Adverse Event Reporting System and FDA Vaccine Adverse Events Reporting System reports, drug labels, and biomedical abstracts to dynamically present the data in an information visualization platform equipped with deduplication and case classification models to inform postmarket safety evaluations.
- 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.
- Developing standardized metadata ontologies to leverage whole genome sequencing 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.

Digital Health

Importance to FDA

Digital health technologies (DHTs) are technologies that use computing platforms, digital connectivity, software, and/or sensors for healthcare and related uses. These

technologies span a wide range of applications from general wellness to medical devices. These products are also used as diagnostics, therapeutics, or adjuncts to medical products (devices, drugs, and biologics). They may also be used to develop or study medical products. DHTs include use of electronic technologies such as artificial intelligence (AI), software as a medical device, and mobile medical applications. The FDA **Digital Health Center of Excellence** is comprised of Agency-wide digital health resources to provide regulatory advice and support to FDA's regulatory review of DHTs.

DHTs are moving healthcare from the clinic to patients by improving understanding of patient behavior and physiology outside traditional clinical settings and enabling early therapeutic interventions. DHTs, such as sensors and other telehealth tools, provide important opportunities in clinical trials to gather information directly from patients at home (decentralized clinical trials), and to gather frequent or continuous medical data from patients as they go about their lives. DHTs can use advanced algorithms, susceptible to potential errors, 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 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.
- The **FDA MyStudies mobile application** enables patients to provide data that can be linked to traditional clinical trials, real-world trials, observational studies, and registries. In 2018, FDA released open source code and technical documentation into the public domain for researchers and developers to customize and rebrand their own clinical trials and studies.

- FDA is collaborating with CERSIs to study the use of DHTs (actigraphy) in patients with heart failure and in children with depression. Actigraphy monitors the human activity/rest cycles 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.

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), administrative claims, registry, and 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. Big data analytics enables researchers to analyze diverse data sources.

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** to build the **National Evaluation System for health Technology (NEST)** with the purpose of driving the quality and efficient use of RWD to inform medical device development and evaluation throughout the entire product lifecycle. 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, sFDA 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 medical 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 is developing and supporting projects that will provide insight into how RWD and RWE can play a role in supporting the evaluation of a product's safety and effectiveness.

Examples

FDA is advancing use of RWE in several ways:

- Funding an **RWE demonstration project**, 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.
- Participating in studies focused on understanding how RWD may be able to inform regulatory decisions with external RWD providers. 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.
- 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 machine learning, for drawing conclusions between the occurrence and causes of an event (i.e., causal inference).
- 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.
- FDA awarded four cooperative agreement grants (from among 31 applications) to explore the use of RWD in generating RWE for regulatory decision-making.

Empowering Patients and Consumers





Introduction

FDA discovers new ways to engage patients and consumers, to better understand the American public's preferences, perspectives, and outcomes. The scope of products regulated by FDA affects consumers and patients, including the veterinary client-patient relationship. Understanding patient, consumer, and VCPR preferences, perspectives and outcomes enables FDA to develop targeted, relevant, 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 actively collects, measures, and analyzes patient and consumer perspectives (e.g., patient preference information (PPI)) to help inform how FDA sets performance goals of medical products, describes the benefit-risk tradeoffs related to medical products for patients with a specific disease or condition, or identifies subpopulations with heterogeneous preferences.

The values, beliefs, attitudes, and cultural factors of consumers, patients, caregivers, and healthcare practitioners play an important role in product development and regulatory decision-making at FDA. 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, design of clinical trials, and rule-making.

FDA characterizes benefit and risk tradeoffs acceptable to patients using medical products and examines consumer understanding of risk statements regarding tobacco products. This includes defining the burden of disease and treatment on patients and their caregivers, identifying patients' unmet needs related to disease treatment, and 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 experience 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 large, formal **Patient-Focused Drug Development Public Meetings** to obtain patients' perspectives on specific diseases and their currently available treatments. 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.
- 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.

- 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 provides 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.

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 on what is important, or from their caregivers, 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):** are 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 gains 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 different activities.

- 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 cataract surgery 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 have the most 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 interviews and surveys to determine how messaging, labeling statements, and claims related to a medicine's attributes affect patients' and consumers' understanding and decision-making.



a more comprehensive picture of how people with diabetes live outside of a doctor's office and showed a need to improve outreach to racial and ethnic minority groups with diabetes.

- 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.

- 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 diverse patient perspectives on living with diabetes. Combining different source data provided

RESEARCH CAPABILITIES, TOOLS, AND RESOURCES





Introduction

Research addressing each of the Focus Areas of Regulatory Science (FARS) is funded through a combination of 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, the Office of Regulatory Affairs (ORA), and the Office of the Commissioner's component offices, as relevant. OCS 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 relevant offices manage 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 move towards application of consistent approaches used to evaluate the impact of research that is conducted or funded by FDA, the Senior Science Council 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 regulatory policies, guidance documents, standards, the **FDA Foods Program Compendium of Analytical Methods**, and review of regulatory submissions through informal guidance and regulatory decision-making on a daily basis.

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, and 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 of Biopharmaceuticals**, clinical outcome assessment instruments, and clinical trial considerations for unmet needs.

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. FDA often partners with standard development organizations to identify and develop **voluntary consensus standards**. The use of 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.

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 **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 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 publicly available **Database for Reference Grade Microbial Sequences** called FDA-ARGOS which provides *refer-*

ence 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 programs.

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.

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

FDA's **Advancing Regulatory Science Broad Agency Announcement (BAA)** 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**. Through the CERSIs, 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 CERSIs 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 Agency-wide regulatory science 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 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 regulatory review, policies, and regulations to develop a skill set relevant to both the review and research areas. Additionally, FDA's **Staff 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.

Professional Development and Continuing Education

FDA provides resources and opportunities for research and review staff to remain up-to-date 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.

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., CERSIs). In addition, researchers attend relevant trainings to stay compliant with regulatory and safety mandates.

Internally, FDA hosts lectures, 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. In addition, the biannual **FDA Science Forum** 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. For example, researchers present how FDA applies science to its regulatory activities in response to a public health challenge during the monthly webcast **FDA Grand Rounds**. FDA also provides **free online trainings** to state, local, and tribal regulatory partners.

Communication and External Meetings

OCS provides strategic leadership, coordination, and expertise, supporting scientific excellence, innovation and capacity to achieve FDA's public health mission. Among its many roles, OCS provides resources to support professional development, training, and collaboration with external stakeholders, while also leading efforts to protect and advance scientific integrity, among other functions, such as supporting science and public health activities to effectively anticipate and respond to counterterrorism.

One way OCS provides cross-agency scientific



coordination (e.g., for emerging technologies, scientific issues involving multiple Agency components, standards coordination, and science communication) is through the SSC and FDA scientific working groups. The SSC provides advice and 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 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 product 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 is tasked with leveraging 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.

Many scientific working groups also undertake 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.

FDA also engages with external partners across the globe to host public workshops, meetings, and conferences covering a wide range of topics such as medical devices, tobacco products, vaccines, 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 efforts 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-3 laboratory suites, animal biosafety level-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 and compliance with applicable laws and regulations regarding laboratory safety, use of animals, human subjects, and select agents. In addition, FDA researchers endeavor to perform research with the highest scientific rigor to support 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. To ensure compliance with safety and other regulatory requirements, staff attend trainings relevant to their area of study on a regular basis.

The **Office of Laboratory Safety (OLS)** partners with center and ORA safety programs to standardize workplace health and safety and laboratory safety programs and provides guidance on safety related issues. The Employee Safety and Environmental Management Staff oversees occupational safety and health including medicine, radiation, biological and chemical safety, and environmental compliance and management. Compliance with the **National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)** as well as hazardous biological agents and toxins is overseen by OLS through FDA's Institutional Biosafety Committee. Likewise, compliance with the U.S. Nuclear Regulatory Commission requirements for working with radioactive materials is overseen by OLS through FDA's Radiation Safety Committee.

At most FDA properties, facilities maintenance and engineering staff conduct preventive maintenance and annual inspections of building equipment and systems and oversee hazardous waste service teams to attend to events such as infectious material spills. Together, FDA and center/ORA staff follow strict safety guidelines and

plans to protect researchers (e.g., Chemical Hygiene and Hazard Communication Plan).

In some cases, FDA research involves use of select agents and toxins, and such use follows requirements of the **Federal Select Agent Program**, including requirements regarding registration to use select agents and toxins. The center or office using these is responsible for the oversight and implementation of the registered work, while the OLS provides general policies for FDA's use of select agents and toxins.

In addition, 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, resolve 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 under 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 50**) and Institutional Review Boards (**21 CFR part 56**).

While FDA strives to **reduce the use of animal tests**, animal tests are still often needed to support development of FDA-regulated products. FDA has three animal programs, 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 obtains 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

3 Rs	Replace, reduce, and refine [the use of animals in research]
3D	three dimensional
AAV	Adeno-associated virus
AE	adverse event
Agency	Food and Drug Administration (U.S.)
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)
C. botulinum	clostridium botulinum
C. diff.	clostridioides difficile
CARB	Combating Antibiotic-Resistant Bacteria
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	Centers of Excellence in Regulatory Science and Innovation (FDA)
CFR	Code of Federal Regulations (U.S.)
CFSAN*	Center for Food Safety and Applied Nutrition (FDA)
CID	complex innovation trial design
CID Program	CID Pilot Meeting Program (FDA)
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)
DHT	digital health technology
DQSA	Drug Quality and Security Act, Public Law 113-54
E. coli	Escherichia coli
ECG	electrocardiogram
EHR	electronic health record
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.)
FTTP	FDA Technology Transfer Program
GSRS	Global Summit on Regulatory Science

HHS	Department of Health and Human Services (U.S.)
HPC	high performance computing
HT	hormone therapy
Lupus	systemic lupus erythematosus
MCM	medical countermeasure
MedDRA	Medical Dictionary for Regulatory Activities
MIDD	model-informed drug development
MIPD	model-informed product development
ML	machine learning
NARMS	National Antimicrobial Resistance Monitoring System for Enteric Bacteria
NASEM	National Academies of Science, Engineering & Medicine
NEST(cc)	National Evaluation System for health Technology (coordinating center)
NCTR*	National Center for Toxicological Research (FDA)
NGS	next generation sequencing
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
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)
OPCTG Program	Orphan Products Clinical Trials Grants Program (FDA)
ORA*	Office of Regulatory Affairs (FDA)
OWH*	Office of Women's Health (FDA)
PBPK	physiologically-based pharmacokinetic
PFAS	per- and polyfluoroalkyl substances
PPI	patient preference information
PPP	public-private partnership
PRO	patient-reported outcome
RCT-DUPLICATE	Randomized Controlled Trials Duplicated using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology
RWD	real-world data
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
SSC	Senior Science Council (FDA)
U-Maryland	University of Maryland
Vet-LIRN	Veterinary Laboratory Investigation and Response Network
VICTRE	Virtual Imaging Clinical Trials for Regulatory Evaluation
WGS	whole genome sequencing
WHO	World Health Organization

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

Stay Connected



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ADMINISTRATION

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