U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Translational Sciences 2022 Annual Report

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From the Director

ShaAvhrée Buckman-Garner MD, PhD
Director

I am proud to share this 2022 Annual Report of the Office of Translational Sciences (OTS). OTS is a super office comprised of five suboffices and the Immediate Office. OTS has a diverse, multidisciplinary team of collaborative and highly qualified professionals who perform a variety of tasks that include, but are not limited to, the following:

- Promoting scientific collaboration and innovation in drug regulatory review across the Center for Drug Evaluation and Research (CDER)
- Assuring the validity of clinical trial design and analysis in regulatory decision-making
- Developing and applying quantitative and statistical approaches to decision-making in the regulatory review process
- Ensuring alignment of CDER research with CDER goals
- Serving the CDER scientific community in establishing technology transfer agreements that are vital to collaboration with the broader scientific community
- Maintaining knowledge management databases that can be the basis of improvements in the regulatory review process
- Overseeing bioavailability/bioequivalence and nonclinical inspections to help ensure the availability of safe and effective new and generic drugs

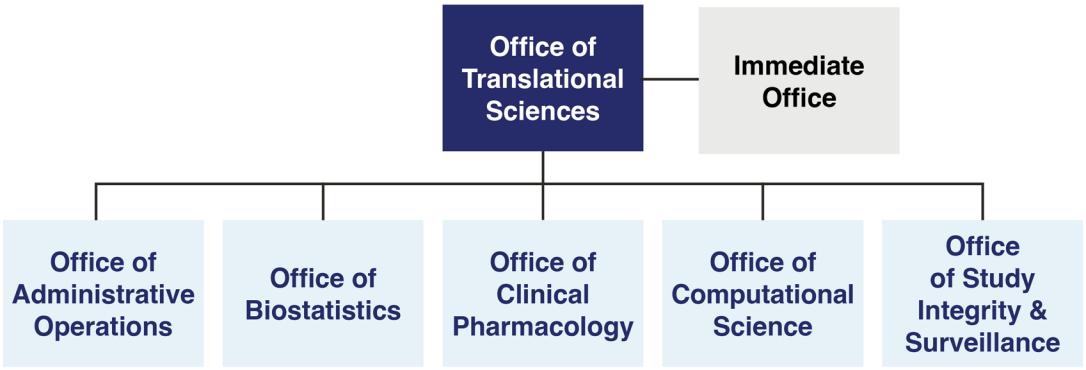
The pages that follow provide examples of some of our important efforts. Where possible, we include hyperlinks to encourage further reading on a given topic presented in the report. As evidenced by the breadth of accomplishments included in this report, staff at OTS work collaboratively to help drive advancements in human health through scientific and regulatory innovation.

Core Functions of OTS

The Office of Translational Sciences (OTS) supports the mission of the U.S. Food and Drug Administration (FDA) through a variety of efforts, including by contributing directly to drug evaluation and supporting the advancement of science by facilitating the conduct of research throughout the medical product life cycle. We perform core regulatory review efforts and applied regulatory research, facilitate scientific collaborations, and manage intramural and extramural research programs. In addition to engaging directly with government and nongovernment entities to develop methods, approaches, tools, and standards to streamline drug development, OTS helps other offices in CDER develop collaborations with non-FDA researchers to stimulate innovation in the development, manufacture, and safe use of drugs.

OTS is guided by its vision, mission, and core values:

OTS Organization Chart



Office of Administrative Operations (OAO)

OAO provides internal customer service support to enable the OTS scientific, medical, and technical staff to focus on our mission with fewer administrative burdens.

Office of Biostatistics (OB)

OB plays a central role in promoting innovative, science-based, quantitative decision-making throughout the drug development life cycle. To support CDER's mission, OB provides statistical leadership, expertise, and advice to ensure that safe and effective drugs are available to the American people.

Office of Clinical Pharmacology (OCP)

OCP advances development of innovative new medicines by applying state-of-the-art regulatory science and clinical pharmacology principles. We promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product life cycle.[1]

Office of Computational Science (OCS)

OCS provides CDER reviewers with innovative, reliable solutions to improve and strengthen the scientific review process by integrating data, tools, and training.

Office of Study Integrity and Surveillance (OSIS)

OSIS ensures that data supporting regulatory decisions are reliable by conducting and directing inspections of bioavailability/bioequivalence and nonclinical good laboratory practice studies submitted to FDA.

Immediate Office (IO)

The IO supports five suboffices in OTS and engages in activities that focus on business transformation strategy; data analytics and technology assistance; data mining; guidance, policy, and communications; health information technology; knowledge management; strategic partnerships and technology transfer; science and research oversight; scientific collaborations; and training and career development.

1 Learn more about OCP through its annual report and the annual report of its Division of Applied Regulatory Science.

OTS Senior Leadership Team

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Raya McCree
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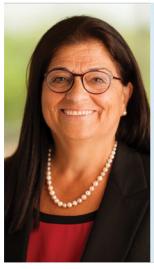

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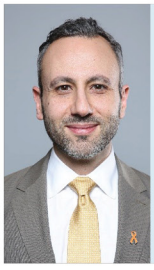

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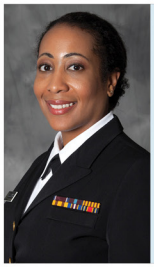

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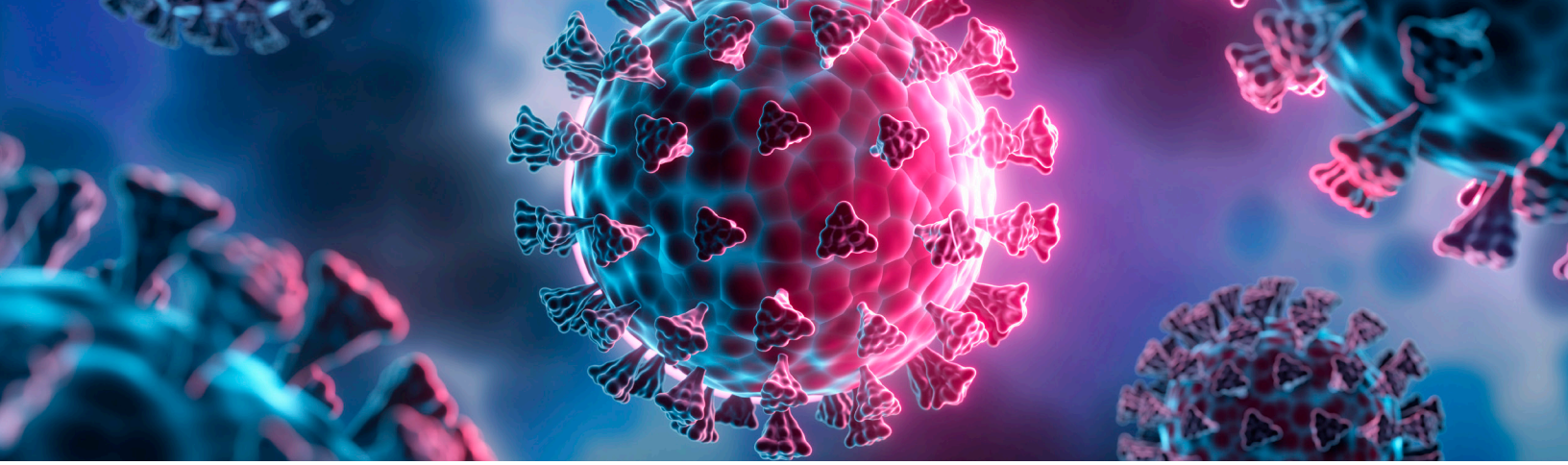

Addressing Public Health Emergencies

COVID-19 Pandemic

OTS continued its efforts to help curb the COVID-19 pandemic. Staff expedited the review of monoclonal antibodies and antivirals by providing drug development guidance, supporting dose optimization, extrapolating data to pediatric populations, developing models, and helping to determine drug product efficacy in the presence of emerging variants. In addition to performing regulatory review, staff participated in regulatory science research on COVID-19 topics such as adverse drug events, therapies that best address the variants of the virus, and the evaluation of drug interactions and toxicity. Below are salient examples of COVID-19-related efforts of OTS staff.

- OTS contributed to the regulatory review of three drugs for treating patients with COVID-19: Olumiant (baricitinib), Veklury (remdesivir), and Kineret (anakinra).
- FDA's Model-Informed Drug Development (MIDD) Paired Meeting Program represents the application of a broad range of quantitative models to facilitate new drug development and regulatory decision-making. The program allows an integration of the current knowledge of disease, pharmacology, and patient characteristics. MIDD provides a unique platform to leverage findings from different sources to address critical questions in drug development.
    - » Developed a mechanistic COVID-19 model to identify potential drug candidates, inform dosing strategies, and guide clinical trial design by quantitatively predicting clinical outcome based on nonclinical data and mechanistic understanding of the disease

- OTS creates and makes available sources of knowledge that enhance operational efficiency and regulatory decision-making. The office also cultivates a variety of dynamic collaborations with internal and external stakeholders to advance solutions to our most pressing challenges.

  - » Shared clinical pharmacology perspectives, up-to-date drug development knowledge, and regulatory actions related to COVID-19 with external stakeholders through nine peer reviewed publications, two listserv communications to over 92,000 subscribers, and seven presentations at national meetings and professional organization venues
  - » Expanded treatment options for patients with COVID-19 by:
    - o Engaging with international regulators to optimize COVID-19 therapies as variants increased in prevalence
    - o Engaging with clinical stakeholders on the use of Paxlovid (nirmatrelvir and ritonavir) in clinical practice, with a focus on patients with renal impairment and the management of potential drug interactions

- FDA's Centers for Excellence in Regulatory Science and Innovation (CERSI) programs foster robust and innovative approaches to advance regulatory science through cutting-edge scientific research. CERSIs may also provide regulatory science information-sharing opportunities, such as lectures, workshops, courses, scholar awards, fellowships, and competitions.

  OTS led multiple projects with several CERSI programs to foster robust and innovative approaches to advance regulatory science through cutting-edge scientific research focused on drug interactions and potential side effects of COVID-19 treatments.

- OTS staff participated in multiple funded projects focusing on COVID-19-related missing data, Bayesian borrowing, and validation of surrogate endpoints.

Substance Use Disorders

In 2022, FDA introduced the Overdose Prevention Framework to undertake impactful, creative actions to prevent drug overdoses and reduce deaths. OTS staff have been contributing to FDA's efforts to understand and end the opioid epidemic. The office engages in innovative research to support primary prevention and harm reduction associated with substance use disorders. Described below are OTS's efforts to address the substance use disorder crisis.

Regulatory Science Research and Innovation

- Acute Pain Pathways (APP) is an OTS-led FDA collaboration with the Yale-Mayo CERSI. FDA collaborators include the Office of Minority Health and Health Equity, CDER Office of New Drugs, and the CDER Office of Surveillance and Epidemiology. The study provides real-world evidence (RWE) in support of FDA's goal to facilitate appropriate prescribing of opioid analgesics by exploring pain trajectories, analgesic and nonpharmacologic treatment use and activity, and health care use of opioid-naïve patients who are prescribed the analgesic for acute pain. Patients representing diverse populations were recruited into the study from multiple health care systems, primary care and urgent care clinics, emergency departments, and dental practices. Data were collected from pharmacy and electronic health records (EHRs), patient-reported outcomes via personal device app, a patient-centered health data aggregation platform and wearable technologies.
    - » Addressed key knowledge gaps in a diverse group of patients with acute pain
        - o Enrolled over 1,400 of the target enrollment of 1,715 (approximate) subjects from 12 states
        - o Published the study's protocol in the July 2022 issue of BMJ Open
- Molecular dynamic simulations are computer-generated predictions of how biomolecules, such as proteins, interact with each other at the atomic level. These simulations contribute to the understanding of biological outcomes.

When applied to the study of biologically uncharacterized opioids, this technology can help assess the abuse potential of the drug and understand possible risks during an emergency public health situation.[2] OTS researchers use the FDA Public Health Assessment via Structural Evaluation (PHASE) methodology, a computational tool that uses the molecular structure of a substance to predict its biological function in the body. PHASE helps evaluate opioids and chemicals with opioid-like properties for the risk these drugs may pose to public safety. The multicomponent computational approach, coupled with expert review, provides a rapid, systematic evaluation of a new drug in the absence of in vitro or in vivo data. The information provided by PHASE can inform law enforcement agencies and the public with vital information regarding newly emerging illicit opioids.

  - » Developed an opioid-related molecular dynamic simulation model to advance regulatory decision-making
  - » Broadened FDA's understanding of opioid pharmacology and reversal of the negative effects of opioids through mechanistic pharmacodynamic modeling and molecular simulation techniques
  - » Used multiple collaborative mechanisms to further scientific and regulatory research to address responses to naloxone as a treatment for opioid overdose

- In the context of substance use disorders, "drug liking" is the amount or concentration of a drug that produces the effects a person desires.[3] Oxycodone is a prescription opioid and is one of the drugs abused in the ongoing opioid epidemic.

  - » Modeled and published, in Pain Medicine, the correlation between oxycodone concentration and drug liking response for immediate-release formulations as they relate to different doses and different routes of administration following manipulation involved in opioid misuse and nontherapeutic use

2 Successes and Opportunities in Modeling & Simulation for FDA (November 2022): https://www.fda.gov/science-research/about-science-research-fda/modeling-simulation-fda

3 https://www.fda.gov/media/150440/download

2022 Achievements

Drug Regulatory Review

A core function in OTS is supporting drug regulatory review, which occurs as part of a multidisciplinary team. Presented below are highlights of OTS's contributions.

- Staff conducted over 10,000 regulatory reviews of drugs submitted by sponsors through Investigational New Drug (IND) Applications, New Drug Applications (NDAs), Biologics License Applications (BLAs), and Abbreviated New Drug Applications (ANDAs). This effort also incorporated the review of drugs already on the U.S. market, which sought to expand treatment options for patients, including new clinical indications, patient populations, and dosing regimens. These reviews resulted in FDA approving 37 new drugs for use by patients.
    - » Engaged sponsors and experts in over 2,000 meetings to optimize drug development plans and study designs (through multiple formats, such as face-to-face meetings, written responses as requested, Advisory Committee meetings, etc.)
- OTS staff met stakeholder needs across CDER, delivering solutions to enhance reviewer effectiveness, and expanding the Center's tools, services, and training to support compliance and inspections, premarket analysis, and postmarket surveillance activities.
    - » Expanded the office's internal data preparation engine to provide automatic, seamless connection with CDER tools and services, making study data accessible to reviewers so they can ensure the safety of drug products and protect public health
    - » Offered a cloud-enabled innovation space for tools, technologies, and data exploration, providing a platform for staff to prototype, test, and implement solutions to CDER's pressing business challenges

- OTS supports research and recommendations on drug labeling through the FDALabel database, which offers a user-friendly interface to search text in drug labels. The drug labels and other drug-specific information on this website represent the most recent drug listing information that pharmaceutical companies submit to FDA.

  - Collaborated with FDA's National Center for Toxicological Research (NCTR) to update the FDALabel database so that it is faster and simpler to use

Innovative Approaches to Advance Drug Development

- The Complex Innovative Trial Design (CID) Meeting Program provides sponsors an opportunity to engage in two additional meetings with FDA to discuss innovative trial designs. The description of each case example referenced below focuses on the clinical trial design that was submitted by the sponsor and discussed with FDA as part of the pilot program. Innovative trial designs help increase the efficiency of clinical trials. OTS leads the CID Meeting Program.

  - Reviewed four designs spanning the therapeutic areas of neurology, oncology, and dermatology

  - Highlighted case examples from the CID Pilot Program on FDA's website and at numerous conferences, including the FDA/Drug Information Association (DIA) Industry Regulatory Biostatistics Forum, the Biotechnology Innovation Organization International Conference, and the DIA Annual Conference

- The MIDD Paired Meeting Program advances and integrates the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources in drug development and regulatory review. OTS leads the MIDD program and accomplished the following:

  - Completed the MIDD Paired Meeting Program under the sixth iteration of the Prescription Drug User Fee Act (PDUFA VI) and oversaw the codification of the MIDD Program under PDUFA's seventh iteration (PDUFA VII)

    - Conducted over 100 internal meetings and nearly 50 sponsor meetings, from 2018 to 2022, under the MIDD Pilot Program

    - Published findings in several areas where model-based methods were applied, including addressing emergent public health needs, informing policy and regulatory paths, characterizing potential biomarkers, tailoring therapies for specific populations, and understanding safety of products and combinations

- Communicated scientific and regulatory advances resulting from the MIDD Pilot Program in four public workshops
  - Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making
  - Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting
  - Model Informed Drug Development (MIDD) for Oncology Products
  - Model Informed Drug Development Approaches for Immunogenicity Assessments

- FDA's Critical Path Innovation Meeting (CPIM) Program provides a pathway for stakeholders, such as industry, academia, other government agencies and consortia, to discuss the science, medicine, and/or regulatory aspects related to innovation and emerging technological advancements in drug development in an informal setting. CDER subject matter experts provide general advice and considerations for how the specific methodology or technology can advance drug development. OTS coordinates the CPIM Program, which has been in existence for 10 years. Some of the topics covered include Patient Focused Drug Development (PFDD), Drug Development Tool (DDT) Qualification, Novel Trial Design, RWE/Real World Data (RWD), Biomarkers, Clinical Outcome Assessment, Pharmacogenomics, Rare Disease Drug Development, Novel Endpoints/New Surrogate Endpoints, New Approaches to Statistical Analysis, and Advanced Manufacturing.

  - Held six CPIMs on innovative topics in drug development:
    - Innovative Conceptual Approaches to Clinical Trial Design and Analysis for an Integrated Research Platform in Non-Alcoholic Steatohepatitis
    - Rare Genetic Dilated Cardiomyopathy
    - Extracellular RNA Splice Variant Biomarker of Myotonic Dystrophy
    - The Use of Digital Pathology in the GLP [Good Laboratory Practices] Environment for Nonclinical Studies
    - The Use of Digitally Measured Nocturnal Scratch in Patients with Atopic Dermatitis
    - Transfer RNA-Based Drugs to Treat Rare Genetic Diseases

Inspections

An important aspect of drug regulatory review is ensuring the welfare of subjects involved in testing a new drug and verifying the quality, study integrity, and regulatory compliance of bioavailability/bioequivalence (BA/BE), nonclinical, and animal rule studies. OTS helps FDA inspect facilities that perform nonclinical studies. Below are highlights of OTS's accomplishments in performing inspections related to drug regulatory review.

Site Evaluations (Inspections and Remote Regulatory Assessments)

- Sites involved with marketing applications generate research data that are critical for the approval of new and generic drugs and therapeutic biologics. Appropriate oversight of the research conduct provides confidence in the information provided. FDA and CDER provide annual Bioresearch Monitoring (BIMO) Inspection Metrics.
    - » Conducted over 1,900 site assessments to determine the need for inspection supporting applications, e.g., ANDA, NDA, BLA, IND
- OTS conducts comprehensive, study-directed, and surveillance inspections of firms that conduct pharmacokinetic, BA/BE, GLP, and Animal Rule studies in support of human drug applications.[4] A remote regulatory assessment (RRA) is a tool FDA uses as an alternative to inspection when travel is limited or when FDA determines that the RRA will assist in the support of regulatory decisions. RRAs may include remote interactions with staff at a study site and remote viewing of electronic systems and facilities.
    - » Evaluated multiple BA/BE and GLP sites via inspection and RRA
- Findings from site evaluations (inspections and RRAs) identify concerns that need further explanation to conclude that the data in marketing applications are reliable.

4 https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-study-integrity-and-surveillance

- » Enhanced inspection site selection tools to centralize and automate the site selection process, ensuring that the most critical sites are identified and inspected
- » Expanded the Inspection Tool Platform to provide additional automation and support for reviewers, making more efficient the process of locating, marking, and sharing data in support of inspection findings

Inspection Tools

- FDA's BIMO Program performs on-site inspections, data audits, and RRAs to assure the quality and integrity of data submitted to FDA in support of new product approvals and marketing applications. The program protects the rights and welfare of human subjects and animals involved in FDA-regulated research. The BIMO Program also monitors drugs after they enter the market to detect, understand, and prevent drug-related problems.[5]
  - » Delivered solutions that streamline the BIMO workflow for reviewers and inspectors throughout the inspections process, automate manual tasks to minimize data entry and redundant processes for BIMO stakeholders, and improve the reliability, accessibility, and timeliness of BIMO data

5 https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/fda-bioresearch-monitoring-information/bioresearch-monitoring-program-information

Science and Research

OTS helps advance CDER's scientific and research initiatives, including providing oversight for intramural and extramural research programs, as well as fostering collaborative efforts to support innovation and reduce scientific uncertainties in the development, manufacture, and safe use of drugs. Highlighted accomplishments include the following:

Advancing Regulatory Decision-Making

- A microphysiological system uses a microscale cell culture platform to model functional features of a specific tissue or organ of human or animal origin. The system resides in vitro, i.e., in a test tube or another laboratory environment. To achieve the modeling of a human/animal tissue or organ, a microphysiological system exposes cells to a microenvironment that mimics the physiological aspects important for their function or pathophysiological condition. The microphysiological system design may aim to provide and support cultured cells with specific properties that define a healthy or diseased organ or tissue function.

    - » Collaborated with model developers to assess microphysiological systems and establish criteria for their qualification, modernize cardiac risk assessment for drug development, answer critical questions related to opioid-induced respiratory depression and response to naloxone of opioid-naïve and chronic-opioid users, and advance qualification of complex in vitro models as alternative methods for animal testing

- A molecular dynamic simulation predicts how biomolecules, such as proteins, interact with each other at the atomic level, contributing to the understanding of biological outcomes. When applied to the study of biologically uncharacterized opioids, this technology can help assess the abuse potential of the drug and understand possible risks during an emergency public health situation.

  - » Developed innovative tools to advance regulatory decision-making, including a cardiac toxicity model, an opioid-related molecular dynamic simulation model, and an interconnected heart and liver microphysiological system

- OTS and NCTR collaborated to explore novel areas for enhancing regulatory review, including research on predictive methods for toxicity as well as the development of tools to enhance the review process.
- Staff improved the operational processes and tracking for clinical monitoring of CDER-funded research using human subjects.
- OTS coordinated the development of the new Alternative Methods program through FDA's Office of the Chief Scientist to assist centers at FDA in implementing Agency-wide programmatic objectives to stimulate qualification and regulatory application of alternative methods to animal testing. The program focuses on opportunities for evolving and innovative technologies to advance useful tools as well as new areas of science to support alternative methods to traditional toxicity and efficacy testing that extend across FDA's product areas.[6]
- Staff at OTS participated in FDA-wide working groups to resolve cross-cutting topics such as biomarkers, -omics (i.e., many areas of research, such as proteomics, genomics, etc.),[7] rare diseases, drug development tools, and individualized therapies.
  - » Collaborated with the Oncology Center of Excellence (OCE), through Project Optimus, to enhance dose optimization for cancer drugs
  - » Participated in R Consortium's R Submission Working Group and developed a pilot to establish the feasibility of using the R statistical programming language for regulatory submissions

    Results are available at https://github.com/RConsortium/submissions-wg—a first step in establishing the deployment of open-source software products.

6 https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda

7 https://www.ncbi.nlm.nih.gov/books/NBK202165/

Scientific Collaborations and Technology Transfer

- Technology transfers include agreements, such as those that allow for collaborations between CDER and industry, nonprofit, government, and domestic and international partners on several cutting-edge research projects. OTS facilitated technology transfers such as the following:

  - » Executed a Material Transfer Agreement that allowed for the transfer of data and materials to and from CDER to define an inflammation biomarker that may predict recurrent pregnancy loss
  - » Facilitated collaboration between CDER and NCTR to evaluate drug-induced liver toxicity using human 3D liver microtissues and other novel approaches
  - » Supported research efforts related to next generation sequencing, which works by looking at a person's DNA to detect genomic variations that may determine whether a person has or is at risk of developing a genetic disease and, in certain cases, may help to inform treatment decisions

- Quantitative approaches have been used to address critical scientific and regulatory issues in all phases of the drug product life cycle.[8] The application of MIDD can leverage large pharmaceutical data sets (big data) available to the FDA and other organizations to improve development and regulatory decision-making.

  - » Facilitated collaboration between OTS and the C-Path's Quantitative Medicine Program to develop a nine-course training module for MIDD

- OTS seeks to cultivate a variety of dynamic collaborations with internal and external stakeholders to advance solutions to our most pressing challenges. This often involves building coalitions that include academia, industry, government, and patient advocates.

  - » Facilitated the collaboration between OTS, CDER's Office of New Drugs, and the C-Path Institute to encourage researchers to share data on kidney safety biomarkers for use in clinical research and drug development

    The collaboration led to a two-day workshop held in May (videos: day one and day two) with individuals in academia, people living with kidney disease or experienced drug-induced kidney disease, FDA staff, and pharmaceutical scientists attending.

8 https://www.fda.gov/drugs/news-events-human-drugs/leveraging-quantitative-methods-and-modeling-modernize-generic-drug-development-and-review-public

» Facilitated CDER staff engagement in multiple public-private partnerships (PPPs), including the International Rare Diseases Research Consortium and the Rare Disease Clinical Outcome Assessment Consortium

These PPPs are in support of the Accelerating Rare Disease Cures Program's focus on the identification of gaps and key issues in rare disease research.

Research Fellowships

- OTS supported the formation of the Translational Sciences Interagency Fellowship (TSIF) collaborative training program, which is jointly sponsored by FDA and the National Center for Advancing Translational Sciences (NCATS). The three-year TSIF program provides training in preclinical translational science, technology development, and regulatory research and review.
- OTS hosted numerous science, technology, engineering, and mathematics (STEM) Fellows in the Oak Ridge Institute for Science and Education (ORISE) program. The ORISE Research Participation Program at FDA is an educational and training program designed to provide college students, recent graduates, and university faculty opportunities to connect with the unique resources of FDA. With the support of an assigned mentor, participants have authentic research experiences using equipment not found on most college campuses. These research experiences complement the educational nature of the programs and make participants aware of potential STEM employment opportunities at the sponsoring agency. Participants have access to unique research and training opportunities, top scientists and engineers, and state-of-the-art facilities and equipment.

Advancing Tools, Technologies, and Innovation

OTS actively seeks to advance the utilization of data, tools, and technologies that yield innovations to enhance regulatory review and regulatory science research. Some salient highlights are listed below.

Enhancing the Efficiency of Drug Regulatory Review

- OTS continues to support staff capacity to enhance drug regulatory review.
    - » Held multiple educational and training forums to inform staff of the most up-to-date advances in clinical pharmacology, innovative technologies, and novel drug platforms, including the Lunch and Learn Technical Seminars Series, Scientific Interest Group presentations, and the Clinical Pharmacology in Drug Development and Regulations course, which is a new reviewer training that included interactive sessions and online courses for 80 registrants in 2022
    - » Built and enhanced solutions that support the Modernization of FDA's New Drugs Regulatory Program by promoting access to quality data and optimizing data analysis capabilities
    - » Provided service-desk capabilities, training events, and analysis services to meet the needs of reviewers of marketing applications

Health Information Technology

- OTS prepared detailed recommendations related to forthcoming regulations on enhancing health information technology systems to augment existing clinical trials data.
- The Common Data Model Harmonization (CDMH) Project aims to accomplish the following: 1) facilitate the use of RWD sources—e.g., claims, EHRs, electronic patient-reported outcomes—to support clinical research and RWE generation; 2) enhance regulatory decision-making; and 3) enhance existing health care and clinical research data standards to support data integration and interoperability. OTS co-led phase I of the CDMH Project with CDER's

Office of Strategic Programs and collaborated with the Office of Surveillance and Epidemiology, Office of New Drugs (OND), National Institutes of Health (NIH), and the Office of the National Coordinator for Health Information Technology. Other collaborators included Elligo Health Research, Yale-Mayo CERSI, University of Chicago, Flatiron, and the Sentinel Operations Center.

In phase II of the CDMH Project, OTS collaborated with NIH, Regenstrief Institute, University of Illinois at Chicago, Elligo Health Research, Digital Infuzion, and OND to leverage the CDMH infrastructure to conduct a standards-based query leveraging RWD to better inform regulatory decision-making.

- OTS reviewed and provided recommendations for the Health Level Seven (HL7) Draft Standards that are aimed at making clinical research data more interoperable with health care data and improve FDA's ability to review RWD in regulatory submissions.

Outreach and Communication Efforts

The following accomplishments are highlights of OTS's outreach and communication efforts.

Guidance and Policy Documents, Snapshots, and Podcasts

- Guidance documents represent FDA's current thinking on a topic. These documents usually discuss more specific products or issues that relate to the design, production, labeling, promotion, manufacturing, and testing of regulated products. Guidance documents may also relate to the processing, content, and evaluation or approval of submissions as well as to inspection and enforcement policies.
    - » Developed multiple guidance documents to communicate FDA's current thinking on a particular regulatory topic or process, which included the following:
        - o Assessing the Effects of Food on Drugs in INDs and NDAs—Clinical Pharmacology Considerations (Final)
        - o Bioavailability Studies Submitted in NDAs or INDs—General Considerations (Final)
        - o Clinical Pharmacology Considerations for Antibody-Drug Conjugates: Draft Guidance for Industry
        - o Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies (Draft)
        - o Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics: Draft Guidance for Industry
        - o Conducting Remote Regulatory Assessments Questions and Answers: Draft Guidance for Industry

- E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential—Questions and Answers (Final, developed under the auspices of ICH)
- General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry (Final)
- General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products (Draft)
- Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling—Content and Format: Draft Guidance for Industry
- M10 Bioanalytical Method Validation and Study Sample Analysis M10 (Final, developed under the auspices of ICH)
- M12 Drug Interaction Studies (Draft, developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH])
- Multiple Endpoints in Clinical Trials Guidance for Industry (Final)
- Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer (Final)
- Population Pharmacokinetics: Guidance for Industry (Final)
- Statistical Approaches to Establishing Bioequivalence (Draft)
- Use of Whole Slide Imaging in Nonclinical Toxicology Studies: Questions and Answers (Draft)

- OTS also contributed to over 40 guidance documents that notably included Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments. This draft guidance document is the third in a series of four methodological guidance documents that describe how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers for use in medical product development and regulatory decision-making.
- FDA's Guidance Snapshot Pilot focuses on a subset of cross-cutting guidance documents on topics that seek to modernize drug clinical trials and accelerate drug development. This pilot program is intended to increase the general public's awareness of and engagement with FDA guidance documents on innovative topics to support the efficient application of the guidance documents' recommendations. In the pilot, each guidance

document is accompanied by a snapshot and a podcast that highlight recommendations using visuals and plain language. The podcasts are interviews with the guidance authors.

  - Published seven Guidance Snapshots and seven Guidance Recap Podcasts to promote FDA guidance documents and their recommendations
  - Launched the publication of Guidance Recap Podcasts on Apple Podcasts

Workshops, Meetings, and Publications

- OTS staff engaged in the following workshops, meetings, and publications:
  - Contributed to multiple meetings on PFDD, which were public meetings with a variety of stakeholders (patients, patient groups, academics, regulated industry representatives, and others) focusing on issues and best practices related to collecting patient input, selecting data collection methods, developing sampling plans and strategies, and data collection and analysis
  - Led efforts to communicate the importance of CDER's research investments to FDA stakeholders through the publication of the What's New in Regulatory Science Newsletter, which reaches over 85,000 subscribers, and the Regulatory Science Impact Stories that report cutting-edge advances made by CDER investigators
  - Published over 250 articles in peer reviewed journals on a variety of topics, including artificial intelligence in real-world applications, Bayesian methods, claims-based algorithms, quality practices of global pharmaceutical manufacturing, drug development, applications of MIDD, safety and toxicity, patient factors, and precision medicine
  - Shared current perspectives and innovative achievements in presentations nearing 300, which were delivered to internal, national, and international scientific audiences on topics such as statistics, biological products/biosimilars, bioavailability/bioequivalence, MIDD, safety/toxicity, patient factors, drug interactions, precision medicine, and general drug development
  - Contributed to the output from the 2020 Symposium held with partners in the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (MHRA): Tackling Challenging Data Integrity Topics in 2020: Update on Good Clinical Practice Perspectives from the US FDA and MHRA UK

- Contributed to the scientific article 2021 White Paper on Recent Issues in Bioanalysis: Mass Spec of Proteins, Extracellular Vesicles, CRISPR, Chiral Assays, Oligos; Nanomedicines Bioanalysis; ICH M10 Section 7.1; Non-Liquid & Rare Matrices; Regulatory Inputs (Part 1A — Recommendations on Endogenous Compounds, Small Molecules, Complex Methods, Regulated Mass Spec of Large Molecules, Small Molecule, PoC & Part 1B — Regulatory Agencies' Inputs on Bioanalysis, Biomarkers, Immunogenicity, Gene & Cell Therapy and Vaccine)
- Led multiple public workshops and webinars on topics including pharmacokinetics in pregnancy, biosimilar, biomarkers, drug disposition in obese patients, and newly published guidance documents
- Interacted regularly with international partners in EMA, World Health Organization, the UK MHRA, and Health Canada, to ensure regulatory alignment and share vital regulatory information
- Partnered with internal and external stakeholders—including NCTR, Pharmaceutical Users Software Exchange, the Clinical Data International Standards Consortium, and BioCelerate—to drive innovation, share knowledge, and build subject matter expertise with a focus on developing solutions to address unmet computational science needs in support of health product development and regulatory review

Abbreviations

ANDA	Abbreviated New Drug Application
APP	Acute Pain Pathways
BA	Bioavailability
BE	Bioequivalence
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
CDER	Center for Drug Evaluation and Research
CDMH	Common Data Model Harmonization
CERSI	Center of Excellence in Regulatory Science and Innovation
CID	Complex Innovative Trial Design
COVID-19	Coronavirus disease 2019
CPIM	Critical Path Innovation Meeting
DDT	Drug Development Tool
DIA	Drug Information Association
EHR	Electronic Health Record
EMA	European Medicines Agency
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug (Application)
IO	Immediate Office
MHRA	Medicines and Healthcare Products Regulatory Agency
MIDD	Model-Informed Drug Development
NCATS	National Center for Advancing Translational Sciences
NCTR	National Center for Toxicological Research
NDA	New Drug Application
NIH	National Institutes of Health
OAO	Office of Administrative Operations
OB	Office of Biostatistics
OCE	Oncology Center for Excellence
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OND	Office of New Drugs
OSIS	Office of Study Integrity and Surveillance
OTS	Office of Translational Sciences
PDUFA VI	Sixth Iteration of the Prescription Drug User Fee Act
PDUFA VII	Seventh Iteration of the Prescription Drug User Fee Act
PFDD	Patient Focused Drug Development
PHASE	Public Health Assessment via Structural Evaluation
PPP	Public-Private Partnership
RRA	Remote Regulatory Assessment
RWD	Real-World Data
RWE	Real-World Evidence
TSIF	Translational Sciences Interagency Fellowship
UK	United Kingdom

Acknowledgments

Thanks to all of the OTS staff whose hard work is represented in the efforts described in this annual report. OTS thanks the following individuals who contributed significantly to the development and publication of this report.

Mitra Ahadpour
Phillip Ames
Shahnawaz Baig
Kimberly Bergman
ShaAvhrée Buckman-Garner
Chekesha Clingman-Henry
Vivianna Cowl
Mary Doi
Malcolm Dennis
Brian Folian
Elizabeth Ford
Mark Geanacopoulos
Vipra Ghimire
Kylie Haskins
Tia Hodge
Terrell Jones
Sean Kassim
Patricia Koussis
Raya McCree
Lauren Milligan
Andreana Nearing
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