U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF COMPLIANCE
OFFICE OF SCIENTIFIC INVESTIGATIONS

Fiscal Year 2022 Annual Report

March 2023

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Executive Summary

The mission of the Office of Scientific Investigations (OSI) is to ensure that products regulated by the Center for Drug Evaluation and Research (CDER) are safe and effective for the life of the product, through oversight and enforcement activities involving:

- the reliability of safety and efficacy data submitted to FDA;
- the application of human subject protection in clinical trials; and
- the FDA requirements for Risk Evaluation and Mitigation Strategies (REMS), Postmarketing Adverse Drug Experience (PADE) reporting, and required postmarketing studies.

Although OSI's mission has remained the same, it is being carried out against the backdrop of rapid change impacting the programs OSI implements and oversees. This includes changes brought on by the COVID-19 pandemic, the effects of which continue to have an impact on OSI's work. For example, changes to the clinical trial ecosystem have accelerated the adoption of modern clinical trial designs, operational approaches, and data sources, and have demanded that OSI adapt quickly to ensure that the data from these trials can be relied on to make regulatory decisions and ensure the protection of trial participants.

These changes and others are occurring in an ever-shrinking world. OSI continues to ramp up its interactions and collaborations with foreign regulatory counterparts to tackle common challenges and learn from each other's best practices. OSI also participates in outreach to stakeholders from industry, academia, and other regulatory agencies and in guidance development activities to proactively promote compliance and protect the public health.

Responding to the challenges and opportunities that come with rapid change requires operational excellence, and to achieve this, OSI co-leads CDER's bioresearch monitoring (BIMO) modernization efforts to increase efficiency and consistency through automation and transparency of the CDER BIMO work processes.

This Annual Report highlights the depth and breadth of OSI's day-to-day work and notable achievements from fiscal year 2022 in support of OSI's mission.

Programs and Organization

What We Do

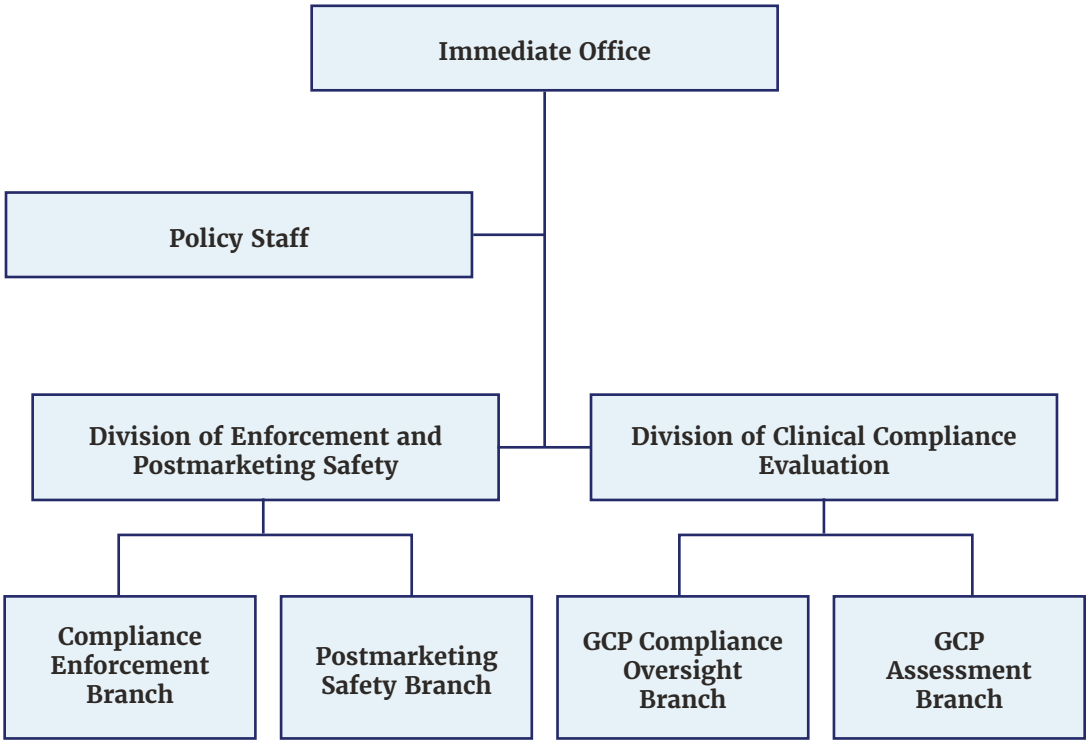
OSI administers the following FDA Bioresearch Monitoring (BIMO) compliance programs and related compliance and enforcement programs for CDER as part of its oversight and enforcement responsibilities:

- Sponsor and Contract Research Organization (CRO)
- Clinical Investigator (CI) and Sponsor-Investigator (SI)
- Institutional Review Board (IRB)
- ClinicalTrials.gov
- In Vivo Bioequivalence and Bioanalytical Studies*
- Good Laboratory Practice*
- Postmarketing Adverse Drug Experience (PADE)
- Risk Evaluation and Mitigation Strategies (REMS)
- Postmarketing Study Requirements (PMRs)

* Responsibility shared with the Office of Study Integrity and Surveillance (OSIS) in CDER's Office of Translational Sciences (OTS)

What is BIMO?
FDA's Bioresearch Monitoring (BIMO) program is a comprehensive, agency-wide program of on-site inspections and data audits, designed to monitor all aspects of the conduct and reporting of FDA-regulated research and oversight of firms' compliance with postmarketing requirements.

Who We Are



Key Metrics and Notable Achievements

OSI administers CDER's BIMO program by directing inspections and remote regulatory assessments (RRAs) of regulated entities to ensure that:

- regulated entities are complying with applicable federal laws and regulations
- data submitted to the agency in support of marketing applications are reliable
- the rights, safety, and welfare of subjects are protected

The following are key metrics and notable achievements from fiscal year 2022 in the program areas that OSI oversees.

Inspections: Roles and Responsibilities
OSI works closely with investigators in FDA's Office of Regulatory Affairs (ORA) to complete inspections. OSI is responsible for selecting sites and issuing inspection assignments that may highlight specific areas of focus. ORA investigators conduct the inspections and share findings with OSI for evaluation. Before, during, and after inspection, ORA investigators and OSI reviewers maintain regular communication to ensure that the inspection objectives are achieved.

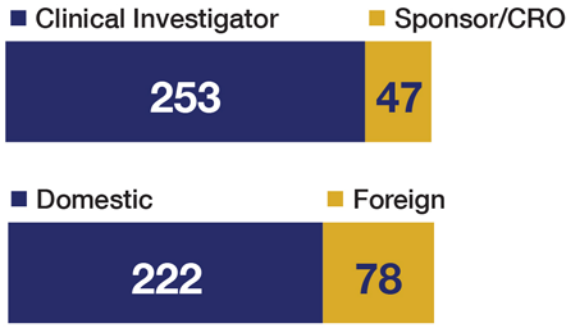
Good Clinical Practice

As part of marketing application review, OSI, in concert with review staff in CDER's Office of New Drugs (OND), determines which sites should be evaluated to confirm the validity of the clinical trial data submitted to CDER. OSI directs inspections and RRAs of sponsors, CROs, and clinical investigators accordingly. OSI uses the ORA inspectional and RRA findings to prepare high-quality, timely reviews called Clinical Inspection Summaries, to assist OND in making decisions on applications and meeting user-fee goals. In addition, OSI conducts collaborative inspections and shares inspectional information with our foreign regulatory counterparts, to optimize regulatory resources and oversight in the evaluation of clinical trial conduct.

Fiscal Year 2022 Highlights

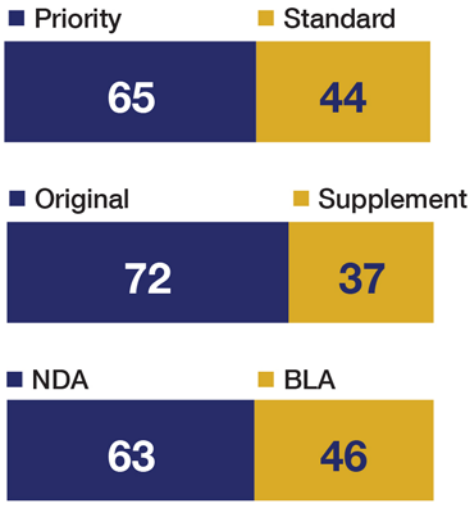
- Jointly published two papers in the scientific journal *Therapeutic Innovation and Regulatory Science* comparing FDA and the European Medicines Agency (EMA) GCP inspection processes and findings and providing insights into the similarities across regulatory agencies.
- Directed 22 inspections in support of five priority marketing applications for COVID-19 therapeutics, including the expanded use of remdesivir, and assisted with reviews for emergency use authorizations (EUAs).
- Directed inspections in support of regulatory decisions for therapies not previously approved or marketed in the United States, targeting a wide range of diseases and conditions.

Inspections in Support of Applications: 300



RRAs: 7

Clinical Inspection Summaries: 109



Foreign Collaborations

Collaborative Foreign Inspections	Reports Shared with Foreign Regulatory Counterparts	Meetings with Foreign Regulatory Counterparts
9	70	26

Human Subject Protection

In support of OSI's mission to ensure that the rights, safety, and welfare of individuals participating in clinical trials are protected, OSI directs the inspections of Institutional Review Boards (IRBs), entities that play a significant role in overseeing the conduct of clinical research. OSI subject matter experts also provide input within FDA and to regulated industry on the interpretation and application of regulations governing the protection of human subjects.

Because IRBs may oversee studies of a variety of FDA-regulated products (for example, drugs, devices, biologics, foods, and tobacco products), OSI collaborates yearly with colleagues in other centers and ORA to select IRBs for inspection. IRB inspections cover all types of FDA-regulated products that the IRB oversees, regardless of the center that leads the assignment.

Fiscal Year 2022 Highlights

- **OSI directed IRB inspections: 42**
- **Human subject protection consults: 4**
  FDA regulations provide a narrow exception to the requirement that the investigator obtain informed consent from each subject, or the subject's legally authorized representative, prior to enrollment in emergency research. This exception enables the study of potential treatments or improvements in the treatment of life-threatening conditions where current treatment is unproven or unsatisfactory, to improve patient outcomes. The regulations provide additional protections for subjects enrolled in these studies. OSI reviews IND submissions for studies proposing an exception from informed consent for regulatory compliance. OSI may also review informed consent documents for regulatory compliance in certain situations.
- **Discretionary certificates of confidentiality (CoCs) issued: 21**
  CoCs help protect the privacy of human subject research participants from whom identifiable, sensitive information is being collected or used by prohibiting their holders (generally researchers) from disclosing that information unless a specific exception applies. Issuance of CoCs is required for certain federally funded research. For other research, potential holders can submit requests to FDA, and CoCs are issued at FDA's discretion, as appropriate. For CDER-regulated research, OSI reviews the requests for discretionary CoCs.

ClinicalTrials.gov

The ClinicalTrials.gov databank provides patients and their family members, health care professionals, and the public with easy access to information about publicly and privately supported clinical studies on a wide range of diseases and conditions. Federal law requires responsible parties to submit registration and summary results information to the ClinicalTrials.gov data bank for certain applicable clinical trials and certify that the requirements have been met. OSI enforces the registration and results information reporting requirements for applicable clinical trials of CDER-regulated products.

Fiscal Year 2022 Highlights

- Issued 20 Pre-Notice Letters. A Preliminary Notice of Noncompliance (Pre-Notice) Letter describes potential violations of ClinicalTrials.gov requirements, and requests responsible parties to take any necessary action to address the potential violations within 30 calendar days.
- Issued a Notice of Noncompliance (Notice) Letter to Ocugen for noncompliance with the ClinicalTrials.gov results information submission requirements. OSI had previously issued a Pre-Notice Letter to Ocugen on July 21, 2021, for failure to submit results information. Ocugen failed to address its noncompliance, despite several follow-up communications. Following OSI's issuance of the Notice Letter, Ocugen came into voluntary compliance with the requirements. This was OSI's fourth Notice Letter.
- Participated in a Clinical Trials Transformation Initiative (CTTI)-led project to identify and explore the key challenges to clinical trial registration and results reporting, and to identify potential solutions. The data will be used to develop best practices and recommendations to support the registration and results reporting process.

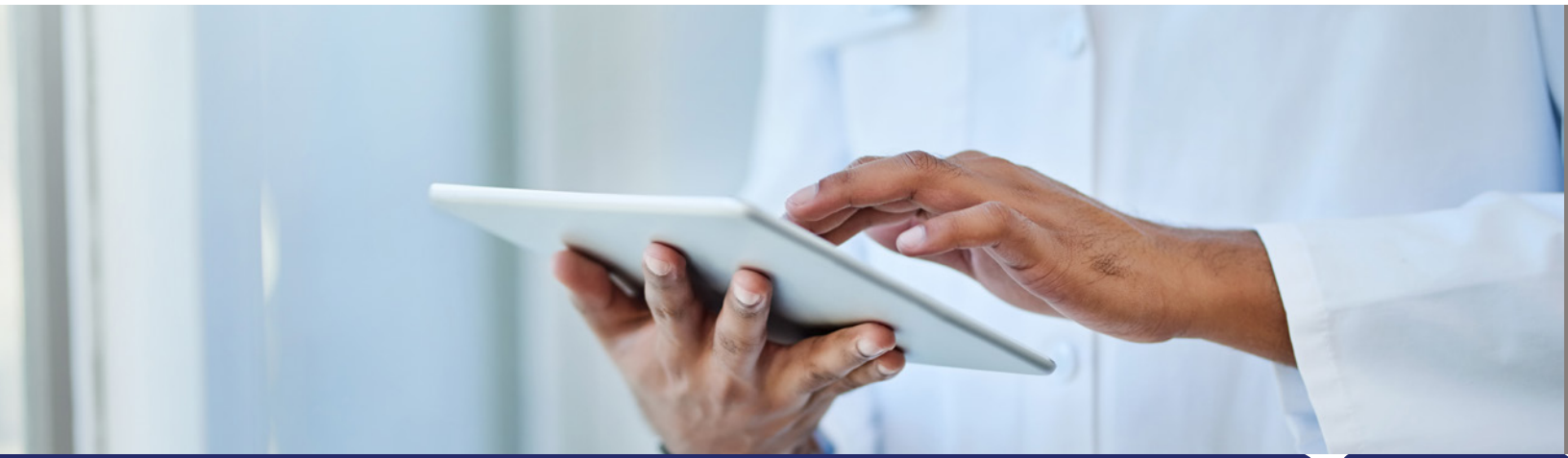
Postmarketing Safety

OSI directs inspections and RRAs to evaluate compliance with risk evaluation and mitigation strategies (REMS) requirements and with postmarketing adverse drug experience (PADE) regulations. OSI also reviews information submitted to the Agency to evaluate entities' compliance with postmarketing study requirements (PMRs). OSI initiates regulatory action when it is warranted. In addition, OSI reviews REMS assessments, reports submitted to FDA by application holders that include analysis, findings, and conclusions related to whether the REMS are meeting their goals. OSI determines if the REMS assessments are complete and timely.

Fiscal Year 2022 Highlights

PADE Inspections	REMS Inspections	REMS Assessment Compliance Reviews
39 (1 RRA)	**14 (1 RRA)**	**38**

- Led quarterly meetings with the United Kingdom's Medicine & Healthcare products Regulatory Agency (MHRA) and Health Canada regarding drug safety compliance programs, to harmonize regulatory requirements and to reduce the burden on the healthcare industry.
- Named chair of the newly established Good Pharmacovigilance Practices (GVP) Expert Circle in the Pharmaceutical Inspection Co-Operation Scheme (PIC/S). PIC/S is a cooperative arrangement between international medicinal product regulatory authorities. Expert Circles are set up by PIC/S to facilitate discussions and the exchange of information among inspectors specialized in a specific area who meet regularly to develop draft guidance, recommendations, and other information, and who offer training in their respective fields of specialization.



Compliance and Enforcement

As part of its compliance function, OSI evaluates referrals (including complaints and required reports) concerning the conduct of clinical trials, and directs inspections of sponsors, CROs, and clinical investigators, as well as IRBs, in response to those referrals, when warranted. OSI also works to bring entities with serious and significant violations of federal laws and regulations into compliance through the issuance of Warning Letters and other administrative actions. The goal of these actions is to promote voluntary compliance with FDA regulations and requirements.

Fiscal Year 2022 Highlights

- Received more than 650 referrals. More than 90 for-cause inspections were conducted to evaluate potential non-compliance.
- Issued a Notice of Opportunity for Hearing (NOOH) to a clinical investigator for repeatedly or deliberately submitting false information to FDA or to the sponsor in required reports. An NOOH is issued as part of the process of disqualifying a clinical investigator from conducting investigational research, and provides the clinical investigator with an opportunity for a regulatory hearing.
- Issued OSI's first Untitled Letter based on regulatory violations identified from an RRA.

Warning Letters Issued		Untitled Letters Issued		Examples of Violations Cited in Warning Letters and Untitled Letters
7		**4**		• **Failure to submit and have in effect an IND** • **Failure to ensure an investigation was conducted according to the investigational plan** • **Failure to ensure that an IRB provided continuing review and approval of a clinical trial**
Clinical Investigator	**5**	**Clinical Investigator**	**1**	
Sponsor-Investigator	**2**	**Bioequivalence-related**	**3**	

CDER BIMO Inspection Modernization

OSI is modernizing the CDER BIMO inspection and compliance operational processes to increase efficiency and consistency through automation and transparency of the CDER BIMO work processes. The CDER BIMO Inspection Modernization Initiative is a portfolio of five separate but interconnected IT projects being developed in collaboration with the Office of Translational Sciences (OTS). The initiative includes:

Workflow management: Workflow management platform for reviewers and management to complete work processes, generate documents, and track and report on activity status.

BIMO system integrations: Bidirectional integration between a cloud-based data hub and data systems to facilitate information sharing and enable access to BIMO information from a central platform.

Inspection site selection: Enhanced inspection site selection tools to centralize and streamline the site selection process, supporting selection decision making and enabling time savings through process automation and reporting.

Database and analytics: Modernized database architecture with new analytics and reporting solutions to support BIMO modernization and enable the preparation of reports and dashboards.

Inspection support tools: Inspection support tools, including a background package line listing generator, to help automate streamline, and facilitate inspections.

Fiscal Year 2022 Highlights

- OSI collaborated with OTS to launch three updated CDER BIMO inspection site selection tools, including the Clinical Investigator Site Selection tool, the Good Laboratory Practice tool, and the Pharmacovigilance Site Selection tool. OSI also updated the FDA IRB site selection tool used by all medical product centers. These next-generation tools are located on a web-based platform and have improved algorithms, data visualization, collaboration, and enhanced analytics.
- OSI works closely with OTS to manage an internal and external Bioresearch Monitoring Information System (BMIS) that contains information on clinical investigators, contract research organizations, and IRBs involved in the conduct of clinical studies conducted under an IND that are listed on a Form 1572 submitted to CDER. In fiscal year 2022, OSI made significant updates to the internal and external database to improve the quality and usability of the data.

Policy

OSI is actively engaged in developing regulations, guidance, and regulatory strategies to advance the BIMO program, as well as the conduct of clinical and nonclinical research and postmarketing safety activities.

Fiscal Year 2022 Highlights

- The publication of multiple guidances addressing the use of real-world data and real-world evidence and digital health technologies underscores FDA's efforts to support innovative clinical trial designs and advances in technology.
- OSI's commitment to global collaboration is reflected in its participation in multiple working groups to update International Council of Harmonisation (ICH) guidelines including:
  - » E2D(R1) Post Approval Safety Data Management: Definition and Standards for Expedited Reporting
  - » E6(R3) Good Clinical Practice
  - » M11 Clinical electronic Structure Harmonize Protocol (CeSHarP)
  - » E8(R1) General Considerations for Clinical Studies (final guidance published April 2022)
- In collaboration with colleagues across FDA, OSI participated in workgroups leading to the publication of several policy documents in fiscal year 2022 (see below).

Data Standards for Drug and Biological Product Submissions Containing Real-World Data, Draft Guidance (Oct. 2021)

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance (Nov. 2021)

Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance (Dec. 2021)

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, Draft Guidance (Dec. 2021)

Conducting Remote Regulatory Assessments Questions and Answers, Draft Guidance (July 2022)

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products, Final Guidance (Sept. 2022)

Institutional Review Boards; Cooperative Research, Proposed Rule (Sept. 2022)

Protection of Human Subjects and Institutional Review Boards, Proposed Rule (Sept. 2022)

Outreach

OSI proactively promotes compliance through clear communication, strategic outreach, and collaboration with external stakeholders. Despite continued travel restrictions, OSI staff conducted internal training activities for staff across CDER and FDA, presented in conferences across the globe, and participated in meaningful stakeholder engagement through virtual conferences and other engagement opportunities, advancing OSI's mission.

Fiscal Year 2022 Highlights

Targeted Training for FDA Staff	Conferences and Outreach Events	Presentations Delivered
20+	25	45

- Hosted a week-long symposium with colleagues from MHRA and Health Canada focused on good clinical practice, good laboratory practice, and good pharmacovigilance practice.
  - » Over 1,800 registrants from more than 40 countries participated, highlighting the critical role OSI holds in proactively promoting compliance in the global arena.
  - » OSI staff participated in 12 presentations throughout the symposium, in a variety of sessions related to good clinical practice and pharmacovigilance.
- Hosted the CDER BIMO GCP Compliance and Enforcement Webinar through CDER's Small Business and Industry Assistance (SBIA) Program. Webinar attendees and YouTube views totaled 5,749, which is a record-breaking total for an SBIA webinar.
- Collaborated with PHUSE, a not-for-profit organization, resulting in the publication of the first-ever Bio-research Monitoring Data Reviewers Guide. This reviewer's guide clarifies for sponsors the expectations when submitting information and datasets to the FDA for planning of BIMO inspections.

Resources

- Agency-wide BIMO Inspection Metrics
- CDER BIMO Inspection Metrics
- Warning Letters and Notice of Violation Letters
- Clinical Investigator Disqualification Proceeding Database
- ClinicalTrials.gov Notices of Noncompliance and Civil Money Penalty Actions
- Bioresearch Monitoring Program (BIMO) Compliance Programs
- Bioresearch Monitoring Information System (BMIS)
- Clinical Investigator Inspection List (CLIIL)
- FDA Inspections Dashboard

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