U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Compliance
Office of Scientific investigations

Fiscal Year 2023 Annual Report

February 2024

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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 protections in clinical trials; and
- the FDA requirements for Risk Evaluation and Mitigation Strategies (REMS), Postmarketing Adverse Drug Experience (PADE) reporting, and required postmarketing studies.

As set forth in the chart below, OSI has identified areas of strategic focus and supporting goals that provide long-range direction to the office, emphasizing areas of core responsibility and opportunities to enhance efficiency and effectiveness to enable OSI to keep pace with a continually evolving industry.

Promote Compliance	**Proactively promote compliance through policy development, clear communication, and collaboration with stakeholders.**		
	Goal 1	Goal 2	Goal 3
	Identify, prioritize, and actively participate in legislative, rulemaking and guidance development to advance OSI interests.	Communicate and engage with FDA and external stakeholders strategically.	Build upon OSI's existing collaborations with FDA, domestic and international partners.
Regulatory & Enforcement Actions	**Optimize and modernize BIMO operations and pursue effective and risk-based regulatory and enforcement actions.**		
	Goal 1	Goal 2	Goal 3
	Conduct risk-based, high-quality, and timely compliance reviews.	Evaluate and optimize the use of alternative tools to FDA inspections.	Successfully develop and implement the CDER BIMO Inspection Modernization program.
Organizational Excellence	**Pursue organizational excellence in workplace culture, human resources, and business processes.**		
	Goal 1	Goal 2	Goal 3
	Create and maintain a culture of engagement, community, and equal voice.	Optimize human capital management.	Support training and professional development of OSI staff.

This Annual Report highlights the depth and breadth of OSI's day-to-day work and notable achievements from fiscal year 2023 in support of OSI's mission and aligned with OSI's areas of strategic focus.

Programs and Organization

What We Do

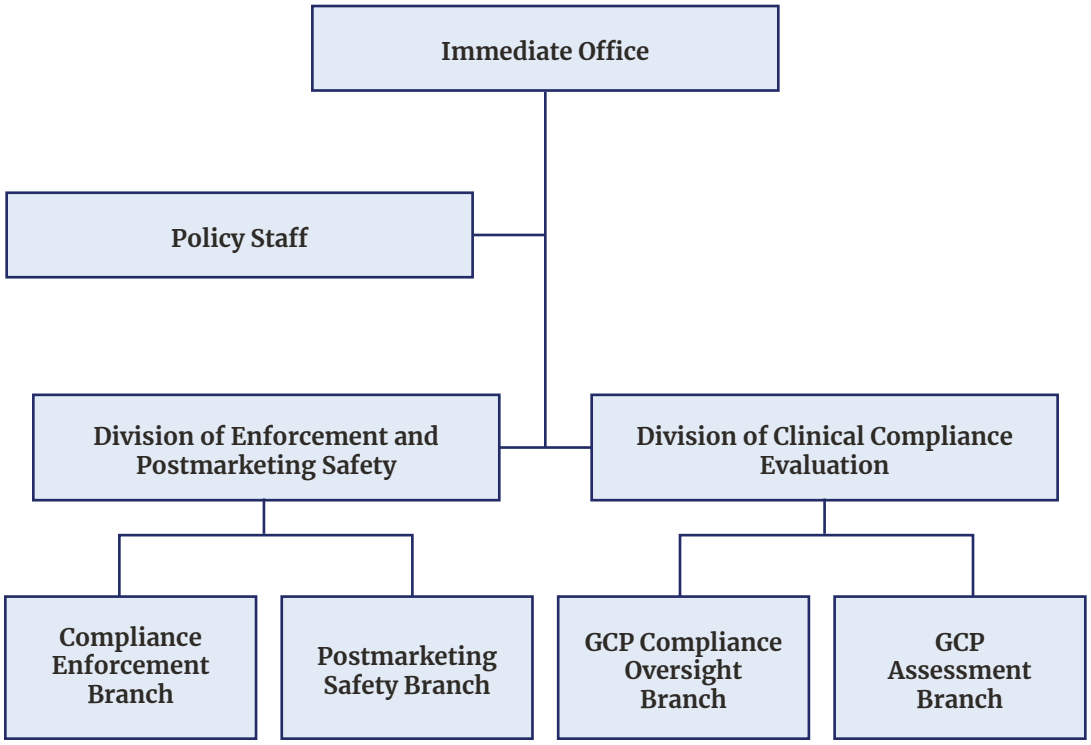
OSI administers the following FDA Bioresearch Monitoring (BIMO) compliance programs and related programs for CDER as part of its oversight and enforcement responsibilities:

- 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 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 assigns and evaluates inspectional operations (on-site inspections and remote regulatory assessments (RRAs)) for CDER's BIMO program 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 2023 in the program areas that OSI oversees.

Good Clinical Practice

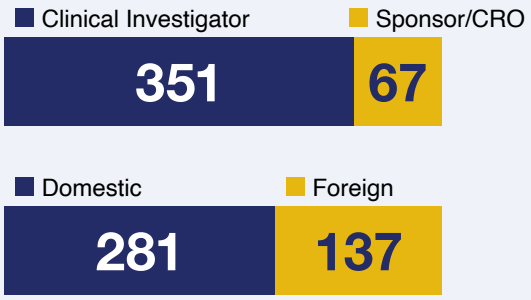
As part of marketing application review, OSI, in concert with review staff in CDER's Office of New Drugs (OND), determines which sites should be evaluated to confirm the validity of the clinical trial data submitted to CDER. OSI assigns inspectional operations of sponsors, CROs, and clinical investigators accordingly. OSI uses the findings to prepare high-quality, timely reviews to assist OND in making decisions on applications and meeting user-fee goals. In addition, OSI conducts collaborative inspections and shares inspectional information with foreign regulatory counterparts to optimize regulatory resources and oversight in the evaluation of clinical trial conduct *(see table on page 4)*.

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 and 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.

Fiscal Year 2023 Highlights

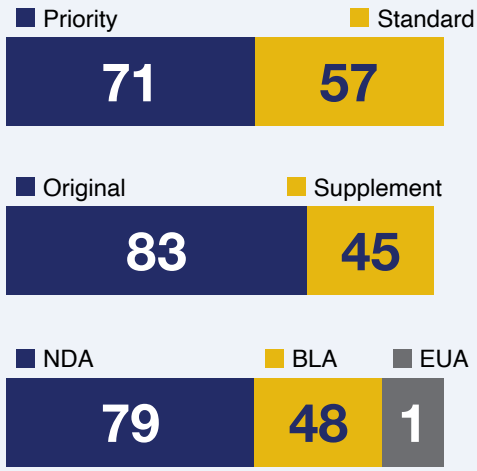
- Published an article in the *Journal of the Society for Clinical Data Management* quantitatively and qualitatively describing FDA's experience using alternative tools to evaluate good clinical practice during the COVID-19 public health emergency.
- Oversaw 16 inspections in support of two priority marketing applications for COVID-19 therapeutics, including Paxlovid, and assisted with reviews for emergency use authorizations (EUAs).
- Oversaw 5 inspections of consumer use studies in support of a first-in-class prescription to over-the-counter switch.
- Completed 128 medical product related consults (Clinical Inspection Summaries) in support of user fee applications received from 24 of the 27 CDER clinical review divisions. The consults resulted in 418 inspectional operations (see table below).

Operations in Support of Applications*: 418



*Includes follow-up inspections

Clinical Inspection Summaries: 128



Foreign Collaborations

Collaborative Foreign Inspections	Documents Shared with Foreign Regulatory Counterparts	Meetings with Foreign Regulatory Counterparts
8	78	20

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 evaluates inspectional operations 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 with other centers and ORA in selecting IRBs for inspection. IRB inspections cover all types of FDA-regulated products that the IRB oversees, regardless of the center that made the selection and leads the assignment.

Fiscal Year 2023 Highlights

- Oversaw **more than 40** IRB inspectional operations. This included **6** RRAs, which were the first IRB RRAs for OSI.
- Completed **5** human subject protection consults evaluating regulatory compliance with requirements for IND submissions proposing an exception from informed consent.
- Issued **16** discretionary certificates of confidentiality (CoCs) to help protect the privacy of human subject research participants from whom identifiable, sensitive information is being collected or used.
- Started a new collaboration with the HHS Office for Human Research Protections establishing standing quarterly meetings to better coordinate and streamline IRB oversight, including standardizing how, when, and what information to share.

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 2023 Highlights

- Issued **32** 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.
- Provided a three-part webinar series, giving a general overview of ClinicalTrials.gov and relevant definitions, laws, and regulations for complying with ClinicalTrials.gov registration and results information submission requirements. Participants gained an understanding of CDER's role and responsibilities with respect to ClinicalTrials.gov oversight and heard examples of compliance and enforcement activities CDER has taken to encourage compliance. The webinar series reached over 9,000 views.

Postmarketing Safety

OSI assigns and evaluates inspectional operations to assess 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 2023 Highlights

PADE Operations	REMS Operations	REMS Assessment Compliance Reviews
45 (1 RRA)	7	27

- Started a pilot to assess the ability of utilizing RRAs to strengthen our ability to monitor industry compliance and inform risk-based inspection planning for planned PADE and REMS inspections as a compliance tool. For this pilot, OSI reviewers conducted the RRA by requesting and reviewing records and documents that are similar to what FDA would request during an inspection.
- Engaged in a variety of collaborative activities focused on advancing the use of novel technology in pharmacovigilance, including leading a sub-group of the PIC/S Pharmacovigilance Expert Circle addressing the use of artificial intelligence and machine learning (AI/ML) in pharmacovigilance with our foreign regulatory counterparts.
- Completed and published updates to the PADE Compliance Program describing processes and procedures for PADE inspections.

Compliance and Enforcement

As part of its compliance function, OSI evaluates referrals (including complaints and required reports) concerning the conduct of clinical trials, and assigns 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 2023 Highlights

- Received more than **900** referrals. As part of the evaluations of these referrals, more than **100** for-cause inspections were conducted to follow-up on potential non-compliance.
- Granted reinstatement of a disqualified clinical investigator's eligibility to receive test articles and to conduct clinical investigations of FDA-regulated products pursuant to the terms of a Reinstatement Agreement.

<table>
<tr><th colspan="2">Warning Letters Issued</th><th colspan="2">Untitled Letters Issued</th><th>Examples of Violations Cited in Warning Letters and Untitled Letters</th></tr>
<tr><td colspan="2">11</td><td colspan="2">2</td><td rowspan="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</td></tr>
<tr><td>Clinical Investigator</td><td>6</td><td>Clinical Investigator</td><td>2</td></tr>
<tr><td>Sponsor-Investigator</td><td>4</td><td colspan="2" rowspan="2"></td></tr>
<tr><td>Institutional Review Board</td><td>1</td></tr>
</table>

CDER BIMO Inspection Modernization

OSI continues to modernize the CDER BIMO inspection and compliance operational processes consistent with FDA's Information Technology Strategic Plan. 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 2023 Highlights

- The CDER BIMO inspection site selection tools are maintained on a web-based platform and used by CDER BIMO to standardize and streamline site selection decisions. The Clinical Investigator Site Selection tool was utilized to process 184 submissions supporting one or more marketing applications. Updates were made to the Institutional Review Board and Pharmacovigilance Site Selection tools, including updating risk ranking scoring and adding new user management functions.
- OSI worked closely with ORA staff to add BIMO compliance program filters to the FDA Inspection Dashboard, including clinical investigator filters, allowing CDER to retire the legacy Clinical Investigator Inspection List in 2024.

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

- Participated in the Advancing Real-World Evidence (RWE) Program and in the Digital Health Technology Steering Committee as part of continued efforts to support innovative clinical trial designs and facilitate the development of drugs, including in areas of medical need.
- Participated in multiple working groups to update International Council of Harmonisation guidelines reflecting OSI's commitment to global collaboration, including:

  E2D(R1) Post Approval Safety Data Management: Definition and Standards for Expedited Reporting
  E6(R3) Good Clinical Practice (draft guidance published June 2023)
  M11 Clinical electronic Structure Harmonize Protocol (CeSHarP) (draft guidance published December 2022)
- In collaboration with colleagues across FDA, OSI participated in workgroups leading to the publication of several policy documents in fiscal year 2023 (see below).

2023 Guidances/Rules

- Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies, Final Guidance (Sept. 2023)
- Considerations for the Use of Real World Data and Real World Evidence to Support Regulatory Decision Making for Drugs and Biological Products, Final Guidance (Aug. 2023)
- Postmarketing Studies and Clinical Trials: Determining Good Cause for Noncompliance with Section 505(o)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act, Draft Guidance (July 2023)
- Use of Whole Slide Imaging in Nonclinical Toxicology Studies: Questions and Answers, Final Guidance (May 2023),
- Decentralized Clinical Trials for Drugs, Biological Products, and Devices, Draft Guidance (May 2023)
- A Risk-Based Approach to Monitoring of Clinical Investigations – Questions and Answers, Final Guidance (April 2023)
- Electronic Systems, Electronic Records and Electronic Signatures in Clinical Investigations Questions and Answers, Draft Guidance (March 2023)
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, Draft Guidance (Feb. 2023)
- Investigational New Drug Applications; Exemptions for Clinical Investigations to Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic, Proposed Rule (Dec. 2022)

Outreach

OSI proactively promotes compliance through clear communication, strategic outreach, and collaboration with external stakeholders. 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 conferences and other engagement opportunities, advancing OSI's mission.

Fiscal Year 2023 Highlights

Targeted Training for FDA Staff	Conferences and Outreach Events	
	Events Attended	Presentations Delivered
25+	25+	35+

- Presented at a 3-day virtual conference hosted by the Society of Clinical Research Associates (SOCRA) designed to aid the sponsor-investigator's understanding of their responsibilities in the conduct of clinical trials. The 3-day conference was held from March 7-9, 2023, and attendees learned about a variety of important topics including the role of quality management systems and clinical quality by design, regulatory requirements regarding source records and data collection, and responsibilities for clinical trials registration and results information submission.
- Participated in meetings with our global regulatory counterparts including the 2023 European Union Good Clinical Practice Inspectors Working Group Workshop where OSI contributed several presentations, and a face-to-face meeting with the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) and Health Canada to share information about good clinical practice inspection approaches, to identify opportunities to promote global industry compliance, and to enhance collaboration with respect to specific cases.
- Spoke publicly in a variety of forums on topics related to the advancement of innovative clinical trial approaches, including presenting at the Drug Information Association conference on real world data and electronic and remote informed consent, participating in a Small Business and Industry Assistance webinar on Electronic Systems, Electronic Records, and Electronic Signatures, and providing an update on CDER's clinical trial modernization efforts to the Society of Clinical Data Managers.

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)
- FDA Inspections Dashboard

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ADMINISTRATION

U.S. Food and Drug Administration
www.fda.gov

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