

The Center for Biologics Evaluation and Research (CBER) Bioresearch Monitoring (BIMO) Program

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Regulatory Education for Industry (REdI) – May 30, 2024

Learning Objectives



- Describe the objectives of the FDA's BIMO Program.
- List three potential triggers for BIMO inspections.
- Describe the inspection process for a BIMO inspection.
- Review current trends in BIMO inspection findings and common violations.
- Identify strategies to prevent noncompliance with FDA regulations.

The BIMO Program



A comprehensive, FDA-wide program of onsite inspections, data audits and remote regulatory assessments designed to monitor all aspects of the conduct and reporting of FDA-regulated research.

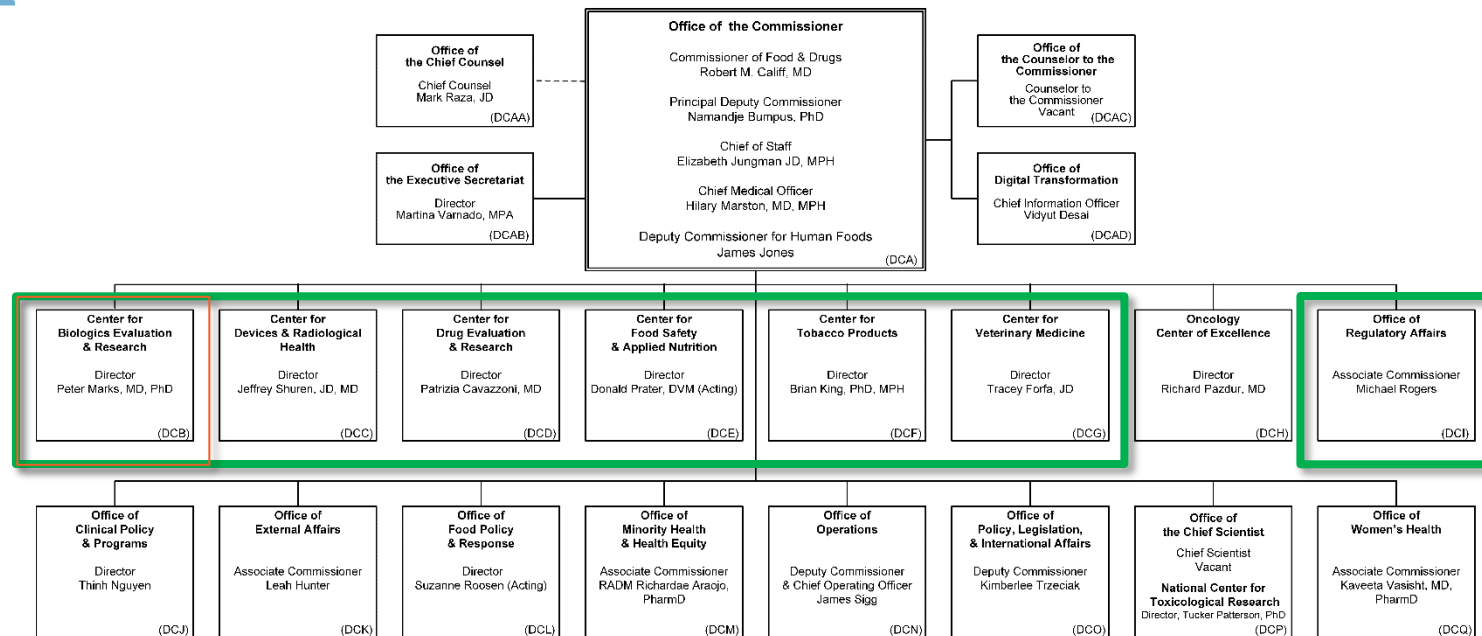
The objectives of the BIMO Program



1. To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;
2. To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and
3. To assess compliance with FDA's regulations governing the conduct of clinical trials.

Department of Health and Human Services Food and Drug Administration

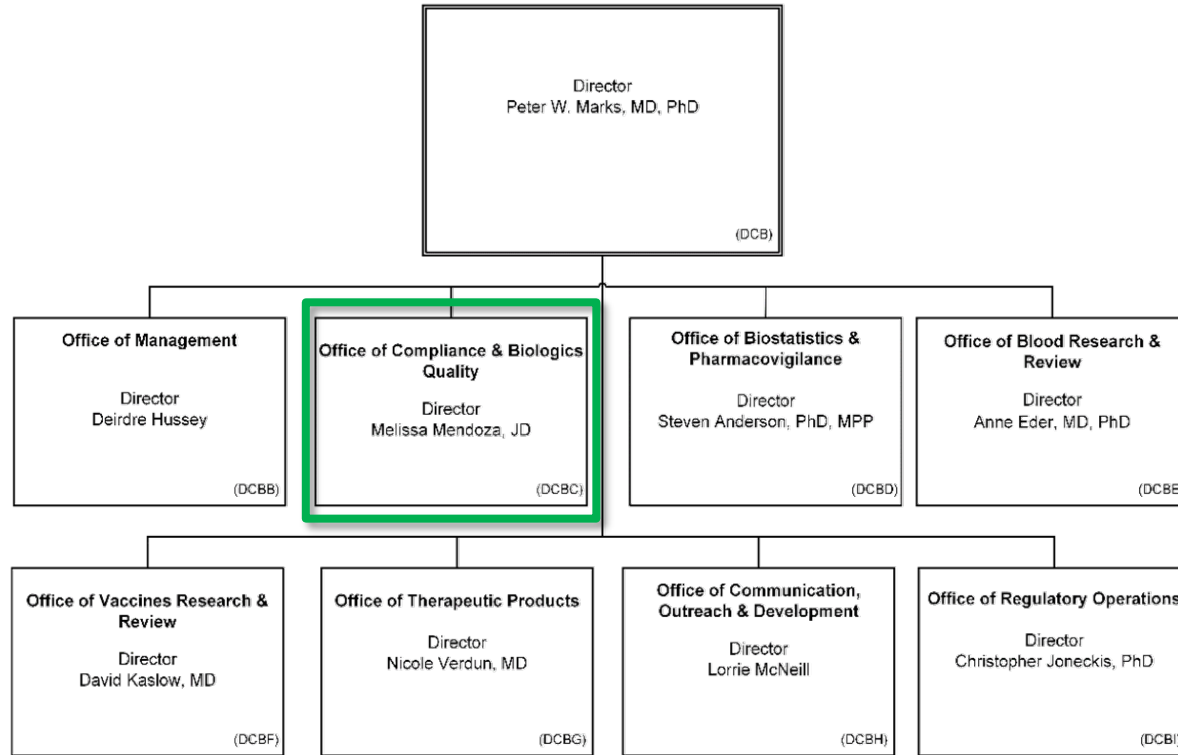
February 2024



Legend:
--- Direct report to DHHS General Counsel

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

February 2024



Regulations Relevant to BIMO



- TITLE 21 CODE OF FEDERAL REGULATIONS
 - PART 50—Protection of Human Subjects
 - PART 54—Financial Disclosure
 - PART 56—Institutional Review Boards
 - PART 58—Good Laboratory Practice for Nonclinical Laboratory Studies
 - PART 312—Investigational New Drug Application
 - PART 314 – Post-marketing Reporting of Adverse Drug Experience
 - PART 320—Bioavailability and Bioequivalence Requirements
 - PART 511—New Animal Drugs for Investigational Use
 - PART 812—Investigational Device Exemptions

BIMO Inspection Compliance Programs



| Program # | Compliance Program Title |
|-----------|--|
| 7348.003 | In Vivo Bioavailability-Bioequivalence Studies - Clinical |
| 7348.004 | In Vivo Bioavailability-Bioequivalence Studies - Analytical |
| 7348.007 | Inspection of Nonclinical Laboratories Conducting Animal Rule-Specific Studies |
| 7348.808 | Good Laboratory Practice (Nonclinical Laboratories) |
| 7348.808A | Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit Inspections |
| 7348.809 | Institutional Review Board |
| 7348.809A | Radioactive Drug Research Committee |
| 7348.810 | Sponsors and Contract Research Organizations |
| 7348.811 | Clinical Investigators and Sponsor-Investigators |
| 7353.001 | Postmarketing Adverse Drug Experience (PADE) Reporting Inspections |
| 7353.001C | Risk Evaluation and Mitigation Strategies (REMS) Reporting Inspections |

BIMO Program Inspections



1. Sponsors
2. Clinical Investigators (CIs)
3. Sponsor-Investigators (SIs)
4. Contract Research Organizations (CROs)
5. Institutional Review Boards (IRBs)
6. Nonclinical and Analytical Laboratories
7. Postmarketing Adverse Drug Experience (PADE)
8. Risk Evaluation and Mitigation Strategies (REMS)

What Triggers a BIMO Inspection?



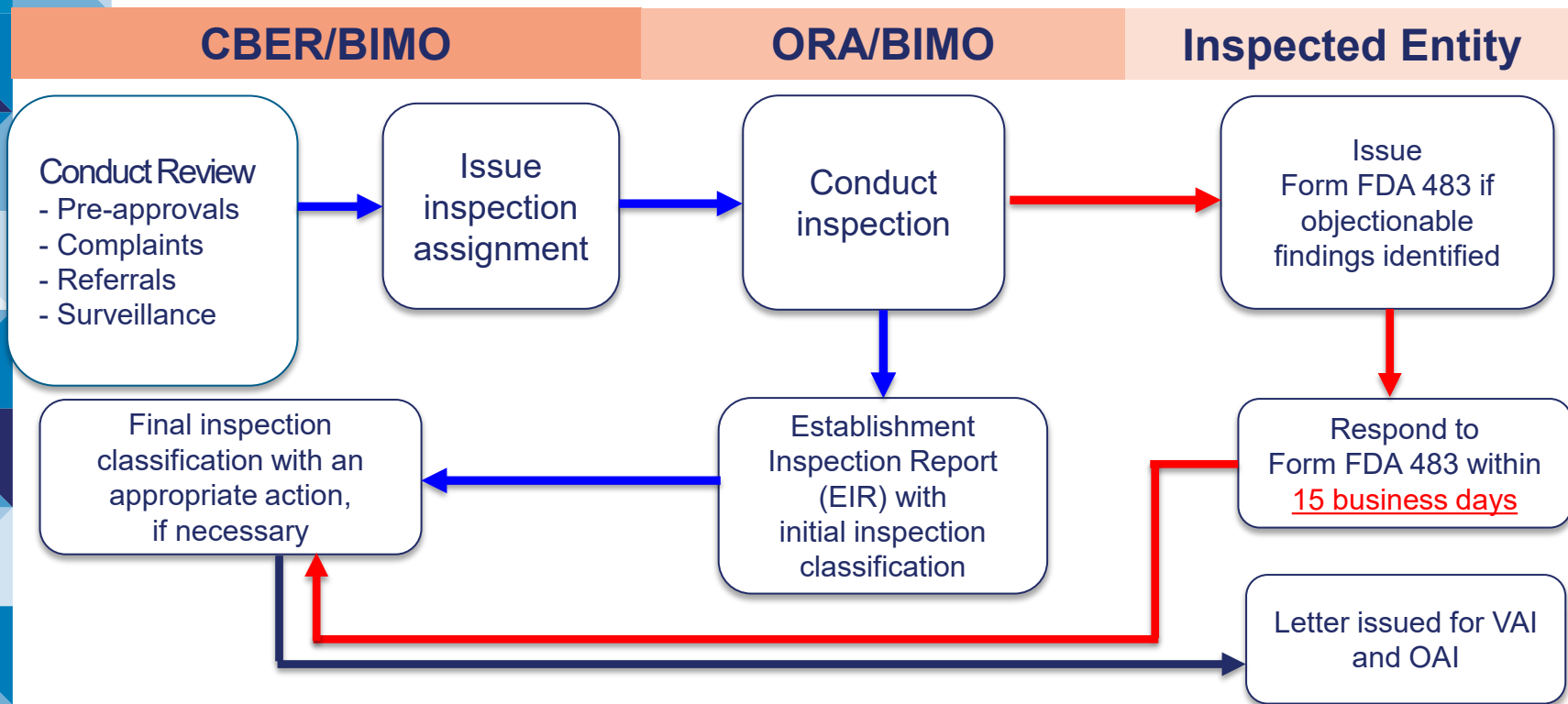
- Marketing Application Driven Inspection
 - Originals (BLA/PMA/NDA)
 - Supplements
- For-Cause/Directed Inspections
 - Primarily initiated in response to complaints
 - Complaints come from any source
- Routine Surveillance Inspections
 - CBER's surveillance of ongoing studies under IND/IDE each year
 - Agency-wide surveillance

What is reviewed during an inspection?



- Patient safety
 - Ensuring that measures are in place to protect the rights, safety, and welfare of participants in the clinical trial.
- Trial conduct
 - Was the study conducted in accordance with the protocol?
 - Did the study conduct adhere to regulatory requirements?
- Data Verification
 - Comparison of sponsor-submitted data with source documents at the site for verification.

General Overview of Inspection Process



Compliance Classifications



Following an inspection, the FDA assesses whether the areas evaluated are compliant with applicable laws and regulations.

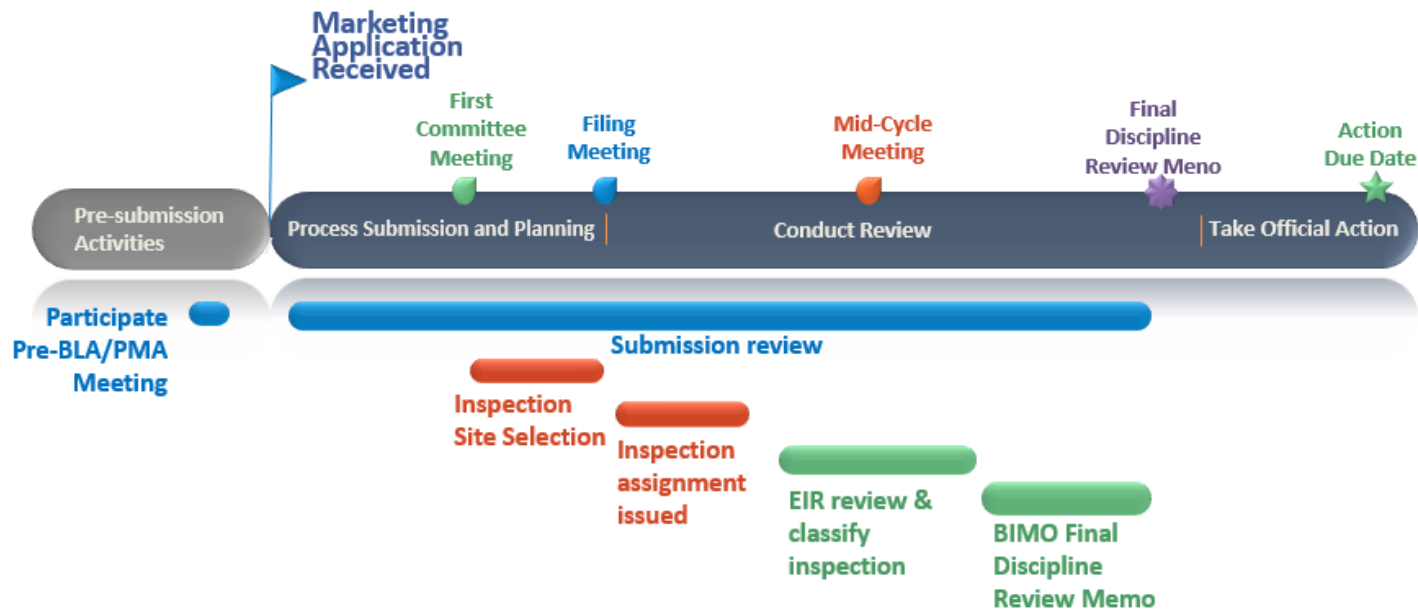
- **No Action Indicated (NAI)**
 - No violations identified
- **Voluntary Action Indicated (VAI)**
 - Objectionable conditions or practices were found but the agency is not prepared to take or recommend any administrative or regulatory action
- **Official Action Indicated (OAI)**
 - Serious noncompliance identified
 - Regulatory and/or administrative actions indicated

CDER's BIMO Branch



- Issue inspection assignments
- Investigate complaints
- Evaluate concerns about data integrity
- Answer questions about Good Clinical Practice (GCP)/ Good Laboratory Practice (GLP)
- Participate in inter and intra center working groups for developing policies and guidance documents
- Conduct internal and external educational and outreach activities to stakeholders

CBER BIMO Reviewer's Roles in Support of Marketing Applications

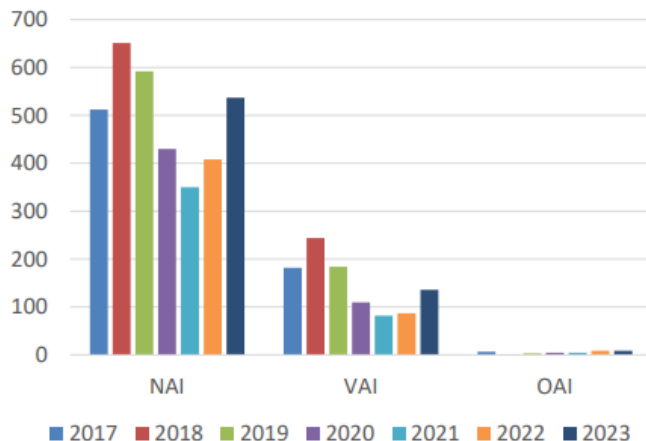


BIMO Inspection Final Classifications by Center – FY 2023*

| <u>Center</u> | <u>CI</u> | <u>IRB</u> | <u>S/CRO</u> | <u>S/I</u> | <u>GLP</u> | <u>BEQ</u> | <u>PADE</u> | <u>REMS</u> | <u>Total</u> |
|---------------|-----------|------------|--------------|------------|------------|------------|-------------|-------------|--------------|
| CBER | 101 | 7 | 10 | 2 | 6 | 0 | 0 | 0 | 126 |
| CDER | 468 | 47 | 65 | 9 | 14 | 133 | 35 | 8 | 779 |
| CDRH | 97 | 16 | 24 | 2 | 2 | 0 | 0 | 0 | 141 |
| CFSAN | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| CVM | 15 | 0 | 4 | 0 | 7 | 0 | 0 | 0 | 26 |
| Total | 681 | 71 | 103 | 13 | 29 | 133 | 35 | 8 | 1073 |

Clinical Investigator Inspection Final Classifications FY 2017-2023

Classifications of Domestic and Foreign Inspections – CI



| | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 |
|-----|------|------|------|------|------|------|------|
| NAI | 512 | 651 | 592 | 430 | 350 | 408 | 537 |
| VAI | 182 | 244 | 184 | 110 | 82 | 87 | 136 |
| OAI | 7 | 1 | 3 | 5 | 5 | 9 | 9 |

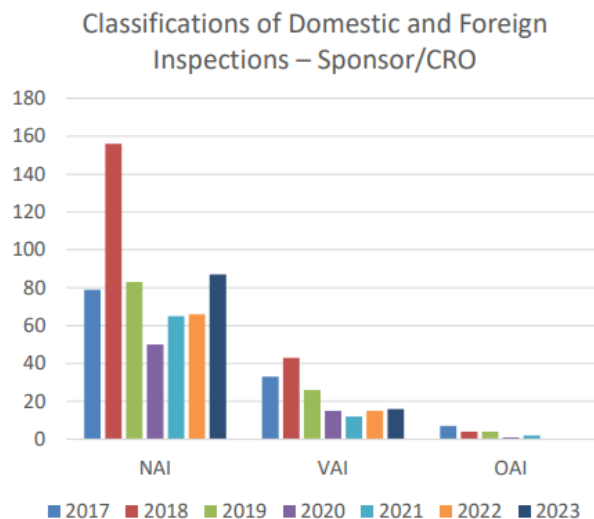
This data is inclusive of all centers' inspections.

Common CI Inspectional Observations*



- Failure to comply with Form FDA 1572 requirements, failure to follow the investigational plan
- Inadequate and/or inaccurate case history records; inadequate study records
- Inadequate subject protection; informed consent issues
- Inadequate accountability and/or control of the investigational product
- Safety reporting; failure to report and/or record adverse events

Sponsor/CRO Inspection Final Classifications FY 2017-2023



| | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 |
|-----|------|------|------|------|------|------|------|
| NAI | 79 | 156 | 83 | 53 | 65 | 66 | 87 |
| VAI | 33 | 43 | 26 | 16 | 12 | 15 | 16 |
| OAI | 7 | 4 | 4 | 1 | 2 | 0 | 0 |

This data is inclusive of all centers' inspections.

Common Sponsor/CRO Inspectional Observations*



- Failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan
- Failure to meet the abbreviated requirements for investigational device exemptions (IDEs)
- Failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; accountability for the investigational product; Investigator Statement (Form FDA 1572); Financial disclosures
- Failure to submit an Investigational New Drug (IND) application; IND safety report
- Failure to submit current list of all participating investigators to FDA at six-month interval after FDA approval of the study

Compliance actions



- NIDPOE/NOOH
- Office of Criminal Investigations Referral
- Warning Letter
- Untitled Letter
- Data Rejection
- Clinical Hold

Suggestions to Prevent Noncompliance



- Before starting the study -

- Understand your responsibilities
- Complete all training required by Sponsor
- Document the delegation of duties
- Develop forms or checklists to make sure all screening tests and study visit activities are performed...even if not provided by the sponsor
- Read the Protocol and amendments thoroughly
- Read the Code of Federal Regulations regarding clinical trials

Suggestions to Prevent Noncompliance



- Before starting the study -

- Develop a plan for organizing records, including transfer of ownership for retirements, illnesses and emergencies
- Train study staff before the study starts and train replacements when staff leave
- Know your limitations
- Obtain the FDA program guidance documents

Suggestions to Prevent Noncompliance



- During the study -

- Track dates when reports are due to IRB and the sponsor
- Promptly report protocol violations and Serious Adverse Events to IRB and sponsor as per the protocol
- Obtain written approval from the sponsor before you do something prohibited by the protocol

Suggestions to Prevent Noncompliance



- During the study -

- Verify that delegated duties are performed, develop a delegation of duties log and stay with it
- Work with Clinical Research Associates
- Correct small problems before they grow
- Use Checklists and Dashboards to track procedures and Dates

Suggestions to Prevent Noncompliance



- After the study -

Organize the Study Records

- To fulfill record retention requirements for possible FDA inspection
- Non-study staff must be able to find all files and binders

Keep them safe, secure and away from harm!

Challenge Question #1



If a Form FDA 483 is issued to the site at the conclusion of the inspection, the site can submit a written response within:

- A. 60 business days
- B. 30 business days
- C. 15 business days
- D. 10 business days

Challenge Question #2



Which of the following is **NOT** a compliance action we can take from a BIMO Inspection?

- A. Warning Letter
- B. Office of Criminal Investigations Referral
- C. Data Rejection
- D. Inspection waiver

Summary



- The FDA's BIMO Program aims to protect participants' rights, safety, and welfare, verify the accuracy of clinical trial data for FDA submissions, and assess compliance with FDA regulations for clinical trial conduct.
- BIMO inspections can occur as a result of a marketing application, complaint, referral, or as part of routine surveillance
- It is a collaborative effort to select, conduct inspections, and implement regulatory actions.
- BIMO inspection and Inspectional Observations metrics are publicly available for each fiscal year.
- Focus on building quality into the clinical trial process through proactive compliance.

Contacts in the Center for Biologics Evaluation & Research (CBER)



CBER's Office of Communication, Outreach, and Development (OCOD)

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- Call:
 - Phone: 800-835-4709
 - Phone: 240-402-8010

Bioresearch Monitoring Branch

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Resources

- [FDA Bioresearch Monitoring Information](#)
- [Clinical Trials and Human Subject Protection](#)
- [BIMO Inspection Metrics](#)
- [Clinical Investigator Status \(Biologics\)](#)
- [Clinical Investigators - Disqualification Proceedings](#)
- [FDA Debarment List \(Drug Product Applications\)](#)
- [Good Clinical Practice Educational Materials](#)
- [CDER BIMO GCP Compliance and Enforcement - 02/16/2022 | FDA](#)