CDRH BIMO Inspections

FDA Small Business
Regulatory Education for Industry (REdI)
Burlingame, CA
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Poll Question

Have you ever had a BIMO inspection?

A. Yes

B. No

C. What does BIMO mean?

Learning Objectives

- Understand purpose and scope of BIMO Program
- Learn about general process of a BIMO Inspection
- Identify documents reviewed during an inspection
- Review top BIMO deficiencies
- Review recent BIMO Inspection metrics and data
- Review CDRH 2018-2020 Strategic Priorities

FDA BIMO Program

- Comprehensive, Agency-wide program
- Provides regulatory oversight for all aspects of conduct and reporting of FDA-regulated research
- On-site inspections and data audits
  - Surveillance and For-Cause/Directed

Who Gets Inspected?

- **Clinical Investigators** (CP 7348.811)
- **Sponsors, Monitors/Contract Research Organizations** (CP 7348.810)
- **Institutional Review Boards** (CP 7348.809)
- **Nonclinical Laboratories** (CP 7348.808)

www.fda.gov/ICECI/ComplianceManuals/CompliancePro gramManual/ucm255614.htm

BIMO Program Objectives

- Protect rights, safety, and welfare of research subjects
- Verify accuracy, reliability, and integrity of clinical and non-clinical trials data submitted to FDA
- Assess compliance with FDA's regulations governing the conduct of clinical and non-clinical trials

CDRH BIMO Inspection Triggers

- Marketing applications
  - PMAs, 510(k)s, HDEs, De Novos
- Early Interventions (Surveillance/Routine)
  - IDE sponsors/CROs/clinical investigators
- New/Novel Technology
- Institutional Review Boards (IRBs)
- Vulnerable Populations
  - pregnant women, children, prisoners, elderly
- Allegations of Research Misconduct/Complaints

Good Research Practices

- Maintain good research practices on a regular and consistent basis
- Don’t start when the investigator calls
- Important for a successful study
- Helps prevent site deficiencies

Good Clinical Research Practices

Adopt a quality system approach to research

- ✓ Qualified Investigators
- ✓ Manage conflict of interest
- ✓ Provide adequate training
- ✓ Ensure clear process for obtaining informed consent
- ✓ Adequate and complete documentation
- ✓ Ensure adequate monitoring
- ✓ Knowledge of applicable regulations:
  - 21 CFR Parts 11, 50, 54, 56 and 812

When FDA Calls

- If the inspection is **not** for-cause, FDA Investigator will:
  - Pre-announce inspection with a phone call
  - Provide proposed inspection dates
  - Provide study that will be inspected
  - Confirm date

- For-cause inspections are not announced


KEEP
CALM
AND
PREPARE

Preparing for inspection

- Notify relevant staff
- Set-up rooms/work space for FDA and study team
- Identify staff to be available during inspection
  - For questions, making copies, etc.
- Ensure study records are organized and available for review
  - Subject research files
  - Regulatory files
- Consider doing a mock FDA inspection

When FDA Arrives

- Greeting
- Show Credentials and provide contact number
- Issue FDA Form 482 Notice of Inspection
- If inspection unannounced, determine:
  - Staff that should be available
  - Reason for inspection
  - Expected timeframe for inspection

BIMO Inspection Elements

- Interviews with research staff
- Tour
- Review of written procedures
- Review of records
- “Daily closeout”
- Final Closeout

During the Inspection

An FDA investigator will verify:

- Informed consent process and subject signatures
- Investigational plan has been followed
- Reporting of adverse events (SAE, UADE, and AE)
- Adequate monitoring
- Case Report Forms match source documentation

Documents Reviewed: Clinical Investigator

- Protocol
- Informed Consent Forms
- Case Report Forms
- Hospital records
- CI Progress Reports
- Sponsor/IRB/FDA correspondence
- Radiological Files
- Laboratory Reports
- Device Accountability Records
- Monitoring Logs
- SOPs
- Adverse Effects
- Protocol Deviations

Documents Reviewed: Sponsor/Clinical Research Org [CRO]

- Training Records
- Case report forms (CRFs)
- Adverse device effect records
- Standard Operating Procedures (SOPs)

Documents Reviewed: Institutional Review Board (IRB)

- Records of IRB membership
- IRB procedures and guidelines
- Minutes of IRB meetings for the past year
- Documents related to the studies:
  - submissions to IRB by CI/sponsor
  - IRB correspondence to CI/sponsor
- Other study related materials

Conclusion of the Inspection

- Closeout discussion with management
- FDA may issue Form FDA 483
  - to most responsible person
- Entity may respond in writing within 15 days
  - **Not required, but strongly suggested**
  - Opportunity to provide clarifications, corrective action, preventive actions, etc.

Response to Form FDA 483

- Response may include the following:
  - ✓ Assessment of ***root cause*** of the problem
  - ✓ An evaluation of ***extent*** of the problem
  - ✓ Any ***corrective actions*** to correct the problem
  - ✓ Any ***preventive actions*** to avoid recurrence
  - ✓ Supporting documentation
  - ✓ Timelines for implementation

Example of Inadequate Response

Observation: Failure to follow the investigational plan.

CI Response:

"I have fired the Study Coordinator and hired a new one with over 10 years experience. Her resume is attached…."

Sponsor Response:

"Our monitors were responsible for ensuring clinical sites followed the study protocol. We have contracted with a new monitor. We do not foresee this failure as a problem in the future."

Example of Adequate Response

Observation: Failure to follow the study procedures.

CI Response:

"We prepared and adopted a written procedure that will help staff to assure compliance with written study protocols and the obligations we accept as clinical investigators for FDA-regulated trials. A copy of the approved SOP is attached.

We have reviewed this new procedure at a meeting held on _____ with all research staff (attendance sign-in sheet attached) and implemented it on _____. After 3 months, we will evaluate these new practices to determine if this corrective action assists with protocol adherence."

After the inspection

- **ORA Investigator**
  - Writes Establishment Inspection Report (EIR)
  - Suggests classification
- **BIMO Reviewer**
  - Evaluates EIR and response
  - Determines final classification and correspondence
  - Conducts discussions with premarket review team during/after the inspection

Compliance Classifications

- **No Action Indicated (NAI)**
  - No or minor objectionable conditions/practices
- **Voluntary Action Indicated (VAI)**
  - Objectionable conditions/practices
- **Official Action Indicated (OAI)**
  - Significant or egregious violations of regulations
  - Repeated violations
  - Sanctions recommended

Possible OAI Outcomes

Untitled Letter (UL) or Warning Letter (WL)

- Depends on classification and severity
- Deviations that significantly impact data quality and/or integrity

Letters intend to:

- Communicate FDA's position
- Achieve voluntary compliance
- Implementation of corrective actions
- Prevent recurrence of deviations

Additional Possible Outcomes

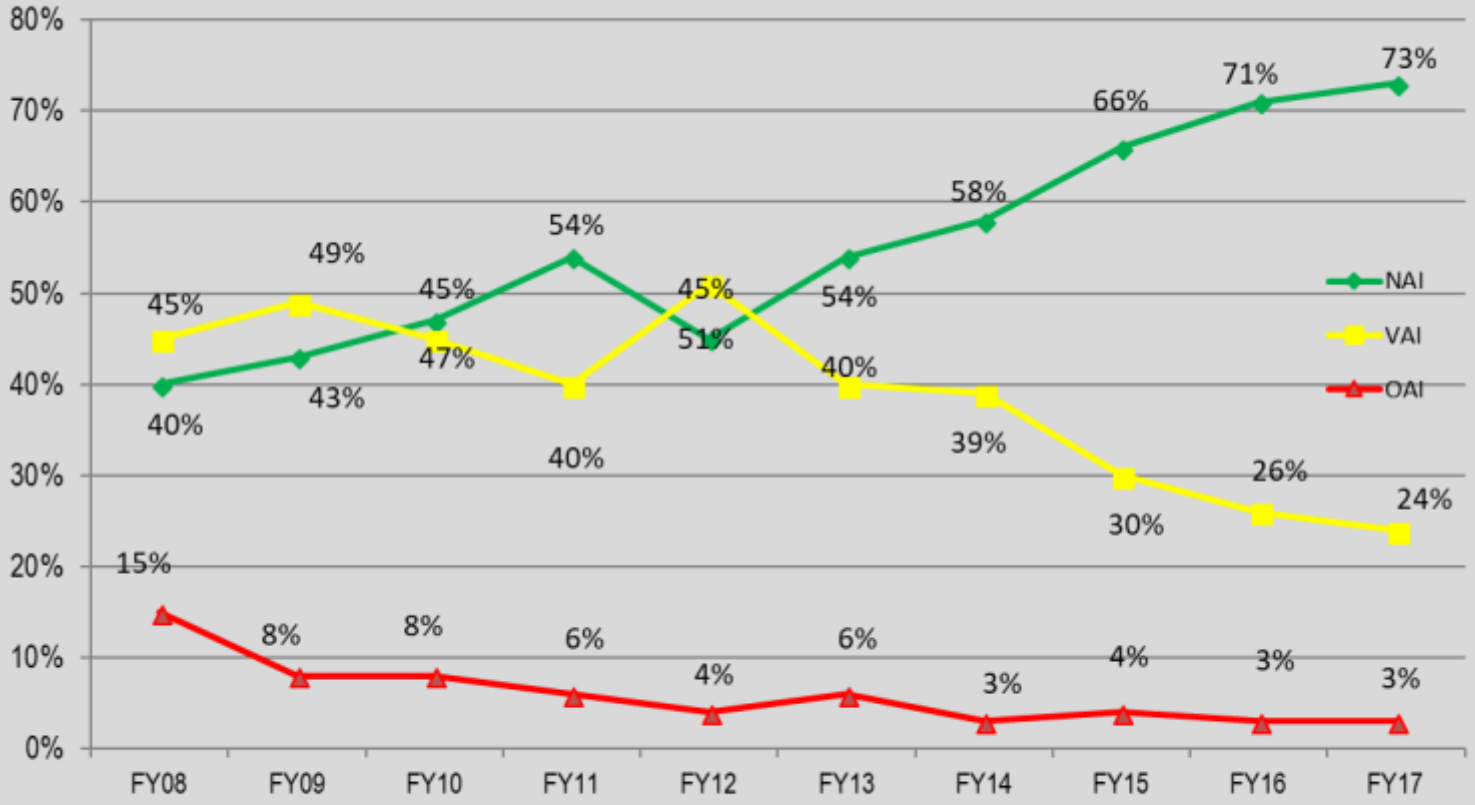
- Invoke Application Integrity Policy (AIP)
- Reject research data used to support a PMA
- Sponsor withdraws 510(k) submission
- BIMO recommends withdrawal of an IDE
- Administrative sanctions to suspend an IRB's authority to approve new studies and/or add new subjects to existing studies

Metrics –
Inspection EIRs Completed

	FY13	FY14	FY15	FY16	FY17
Sponsor	53	42	43	48	47
CI	193	214	226	198	199
IRB	76	61	42	35	35
GLP	10	7	1	5	6
Total	332	324	312	286	288

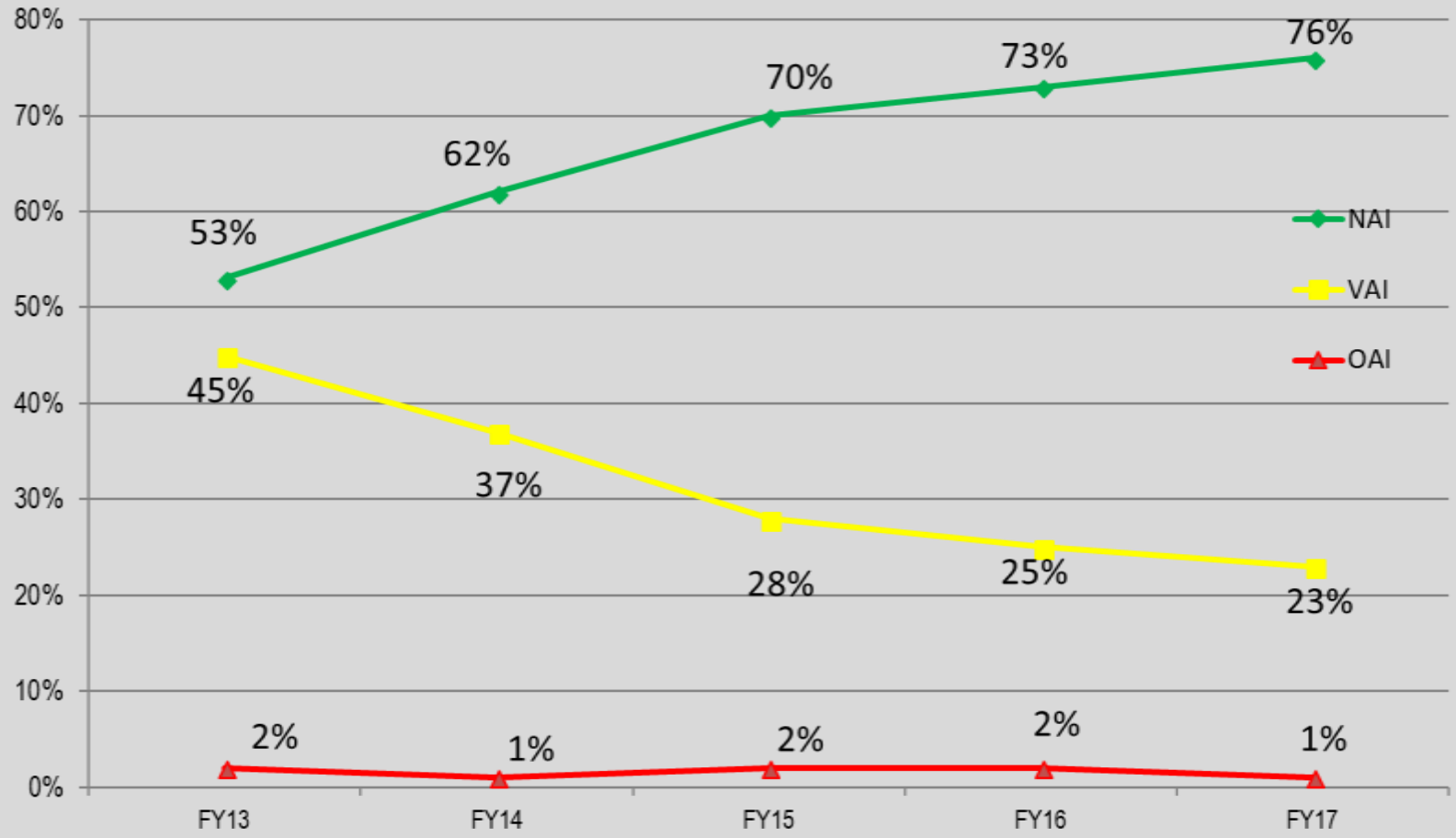
FY13 - FY14 Number of assignments issued
FY15 - FY17 Number of assignments classified

Metrics –
Classification Trends



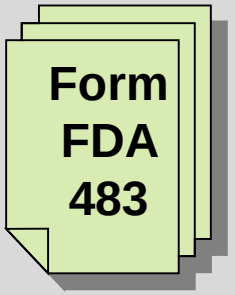
FY13 - FY14 Number of assignments issued
FY15 - FY17 Number of assignments classified

Classification Trends - CI



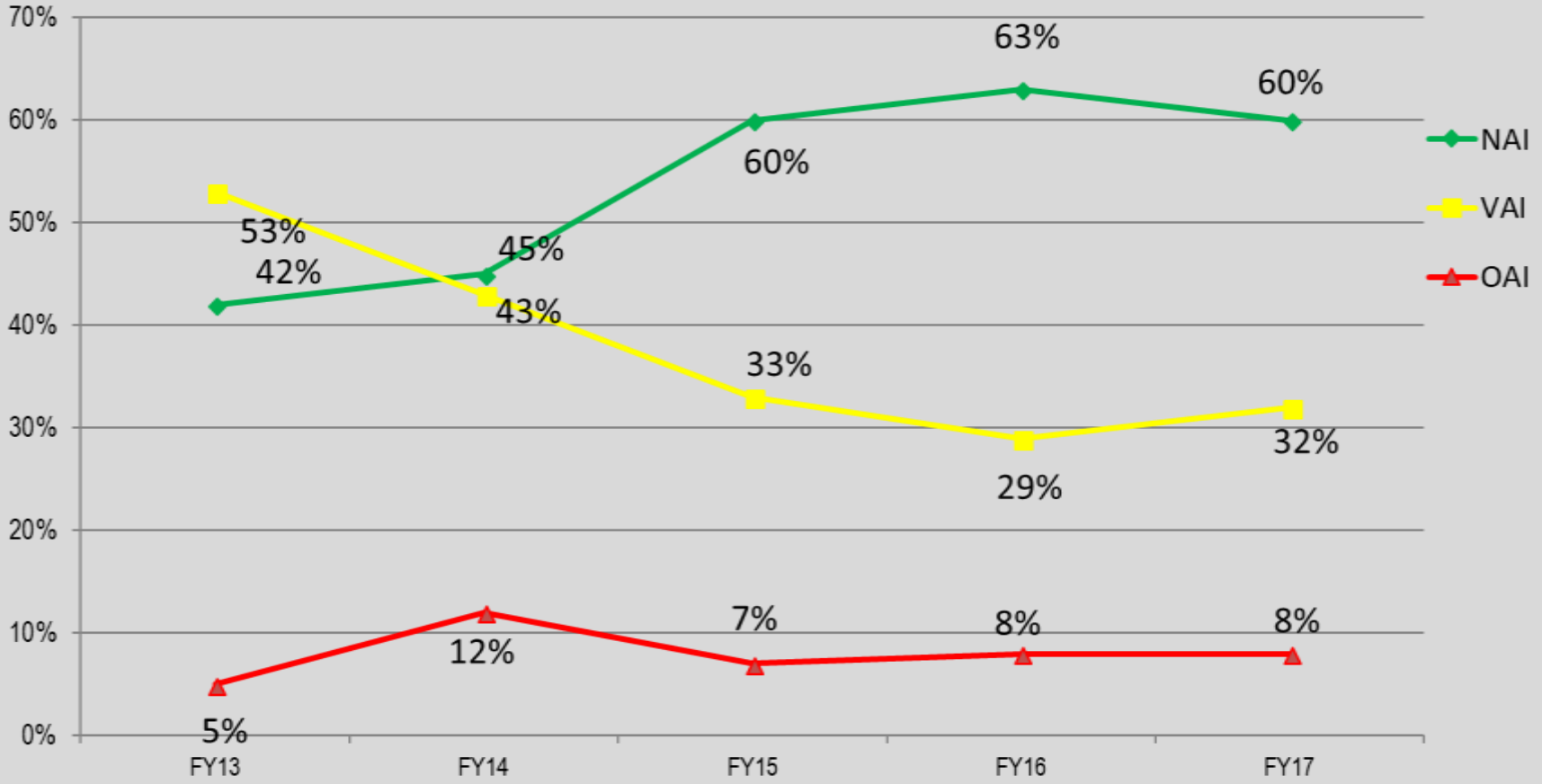
FY17: 199 EIRs Completed

Top Clinical Investigator Deficiencies



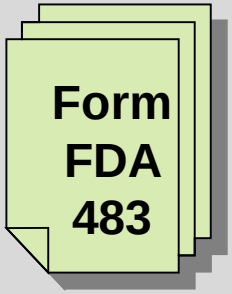
CFR Regulation	Description
812.110(b)	Investigator non-compliance with agreement, plan, and/or regulations
812.140(a)	Investigator's subject records are inadequate or lack informed consent
812.100	General responsibilities of investigators
50.27(a)	Consent form not provided, approved, signed or dated
812.110(a)	Informed consent obtained prior to study approval

Classification Trends - Sponsor



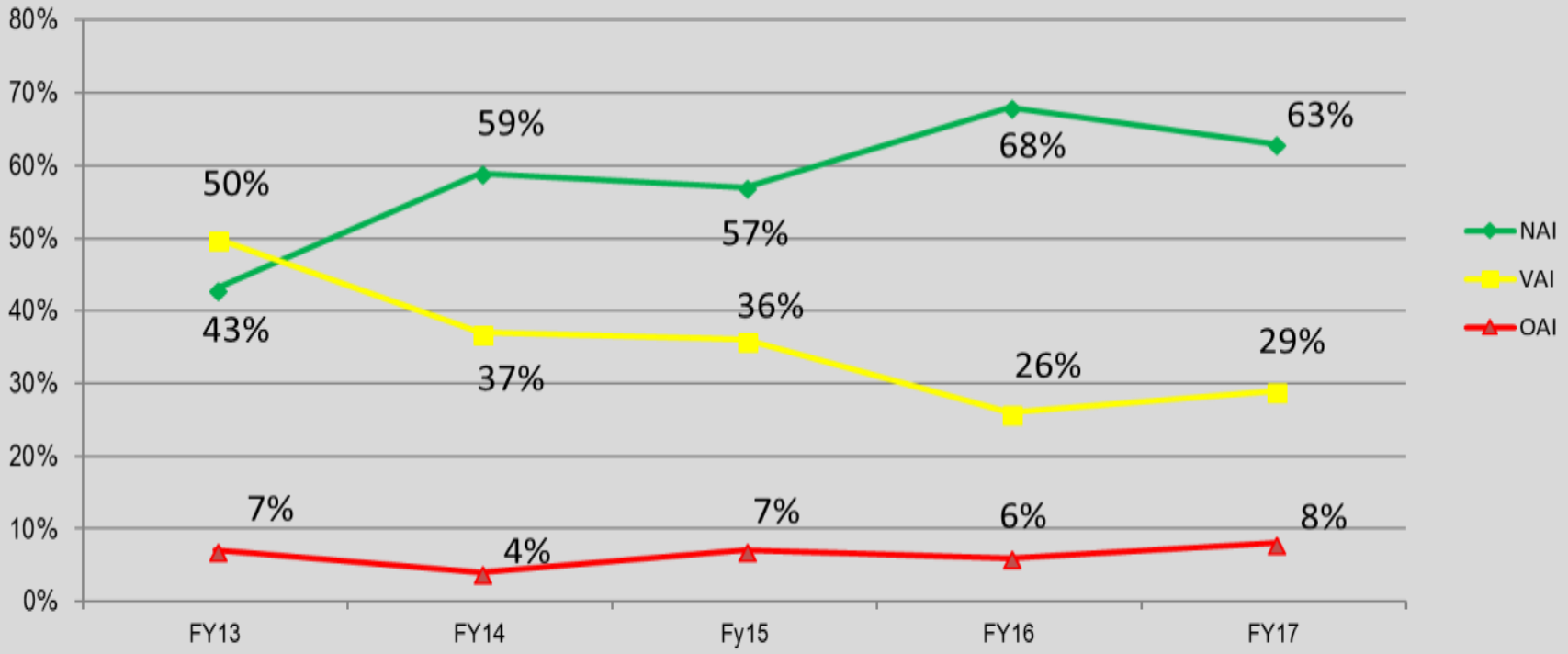
FY17: 47 EIRs Completed

Top Sponsor Deficiencies



CFR Regulation	Description
812.46(a)	Sponsor's failure to secure investigator's compliance/device return/disposal or comply with agreement
812.140(b)	Sponsor correspondence records, device shipment, disposition, or investigator agreement incomplete, inaccurate or lacking
812.40	General duties of sponsors
50.27(a)	Consent form not provided, approved, signed or dated
812.43(c)	No investigator agreement; no financial disclosure

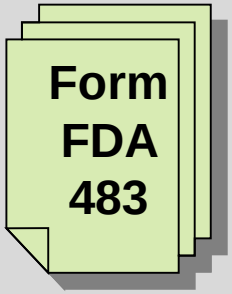
Classification Trends - IRB



FY17: 35 EIRs Completed

Top IRB Deficiencies

CFR Regulation	Description
56.115(a)	Minutes of IRB meetings/List of members
56.108(a)	Reporting findings and actions to investigator/ institution/ initial and continuing reviews/prompt reporting of changes
56.108(c)	Approval from a majority of members present/ Members present for review
56.111(a)	IRB determination of informed consent sought from subjects or representatives, or informed consent documented
56.108(b)	Prompt reporting of noncompliance/ Reporting of suspension/termination



CDRH 2018-2020 Strategic Priorities

FDA Resources

- **CDRH Homepage**
  www.fda.gov/MedicalDevices/default.htm

- **CDRH Learn**
  www.fda.gov/training/cdrhlearn/default.htm

- **Device Advice**
  www.fda.gov/MedicalDevices/DeviceAdvice

- **FDA/ORA BIMO Information Page**
  www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm

- **BIMO Compliance Manuals**
  www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614.htm

- **CDRH 2018-2020 Strategic Priorities**
  www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM592693.pdf

Summary

1. BIMO conducts on-site inspections and data audits, both surveillance and for-cause / directed.

2. Preparation is key to a successful inspection.

3. Preparation includes good research practice on a regular and consistent basis.

Questions?

Contact Information

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CDRH BIMO Inquiries, Complaints, IRB reports

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Please evaluate this session:

surveymonkey.com/r/DEV-D1S03

Call to Action

- Preparing for an FDA inspection starts with good research practices.
- Good research practices help to develop quality medical devices for patients.


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