Bioresearch Monitoring

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Topics

- BIMO Program
- Inspections
- Compliance Metrics

FDA BIMO Program

- On-site inspections
- Data audits

Monitor FDA-regulated research

Program Objectives

- Protect the rights, safety, and welfare of human research subjects
- Ensure the quality and integrity of research data

CDRH BIMO

- Audits clinical and nonclinical data
- Coordinates inspections/investigations
- Coordinates application integrity cases
- Reviews promotion and advertising claims
- Initiates regulatory actions
- Conducts educational outreach

Inspection Sites

- Sponsors/Monitors (S/M), Contract Research Organizations (CROs) or Other Third Parties
- Clinical Investigators (CIs)
- Institutional Review Boards (IRBs)
- Nonclinical Laboratories

Inspection Triggers

- Marketing application
- Novel technology
- Vulnerable population
- Surveillance
- Complaint
- Previous violative inspection

Inspection Purpose

- Monitor compliance with regulations
  - Human subject protection (21 CFR 50 & 21 CFR 56)
  - Clinical study conduct (21 CFR 812)
  - Good laboratory practices (GLPs) (21 CFR 58)
- Verify accuracy of data
- Address special issues

Pre-Inspection

- Gather background information
- Issue assignment memo
- Schedule inspection

Inspection Process

- Issue inspection notice
- Review & collect records
- Interview relevant staff
- Discuss inspection proceedings and findings

Inspection Questions (1)

- Does data match source documents?
- Was IRB approval obtained?
- Was FDA approval obtained?
- Was informed consent obtained?
- Was the device labeled appropriately?
- Was the device promoted?

Inspection Questions (2)

- Was the study protocol followed?
- Was the study monitored?
- What activities were undertaken to assure the quality and reliability of the data?
- Are device records accurate and complete?
- Are study records accurate and complete?
- Were required reports submitted?
- ??

Inspection Closeout

- Discuss final observations
- Issue Form FDA 483 “Inspectional Observations,” if needed

What should you do if you receive a 483?

RESPOND!!

- Take prompt corrective actions
- Submit a response within 15 working days

Written Responses

- Root cause of the problem
- Extent of the problem
- Corrective actions
- Preventative actions
- Timelines for implementation
- Supporting documentation

Response Do's and Don'ts

- Leave out finger-pointing / blame game
- Don't just say, "I'm sorry. I won't do it again."
- Say what you *CAN* and *WILL* do
- Know what the response says
- Ensure CIs know what they (i.e., you on their behalf) proposed

Post-Inspection

- Submit Establishment Inspection Report (EIR)
- Review EIR, exhibits, and response
- Classify inspection
- Issue correspondence
- Initiate follow-up actions

Inspection Classifications

- No Action Indicated (NAI)
- Voluntary Action Indicated (VAI)
- Official Action Indicated (OAI)

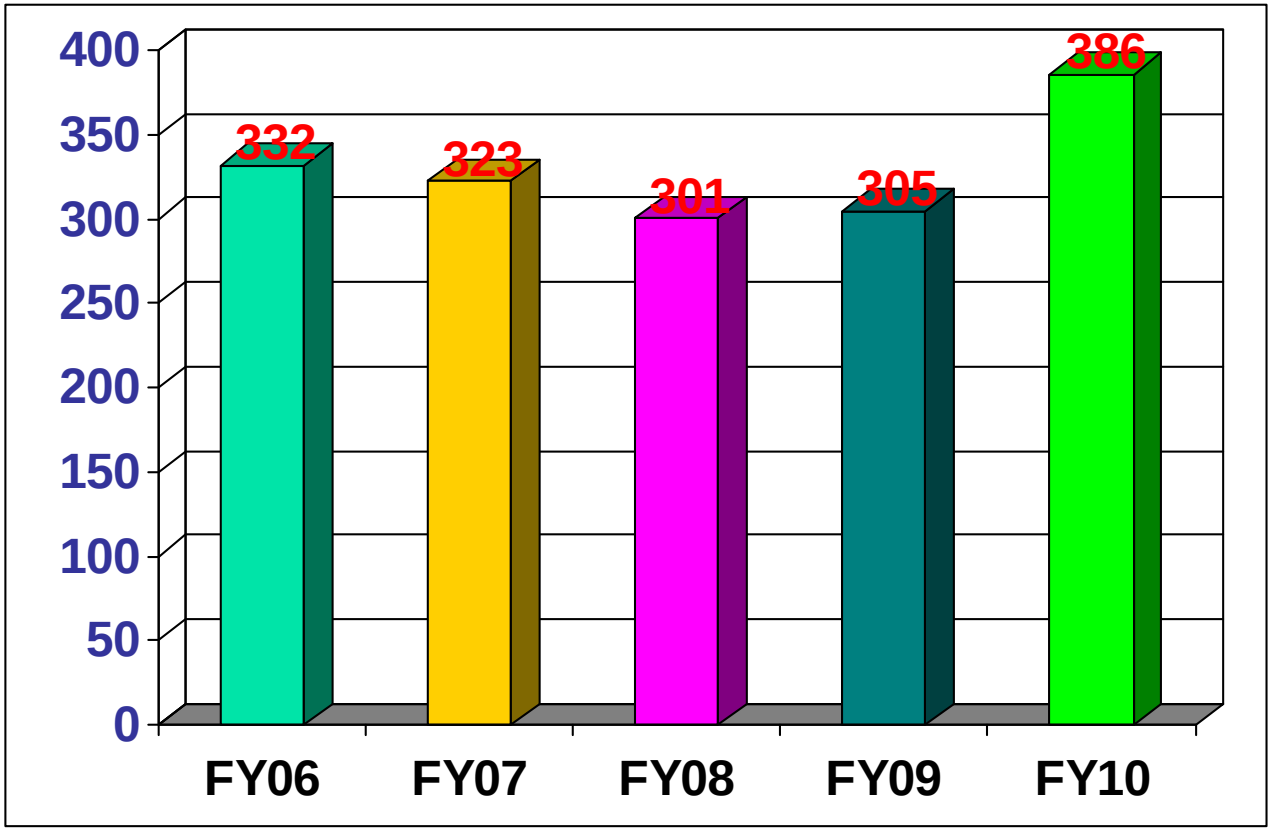
FDA Regulatory Actions

- Rejection of data
- Deficiency letter
- Withdrawal of submission
- Untitled letters
- Warning letters
- Consent Agreement
- Disqualification
  - CI, IRB, GLP
- IRB restrictions
  - No new studies/subjects
- Application Integrity Policy (AIP)
- Civil Money Penalties
- Seizure / Detention
- Injunction
- Criminal Prosecution

Challenges with IVD Studies

- Use of leftover specimens
- IRB review and approval
- IDE-exempt studies
- Limited citable violations

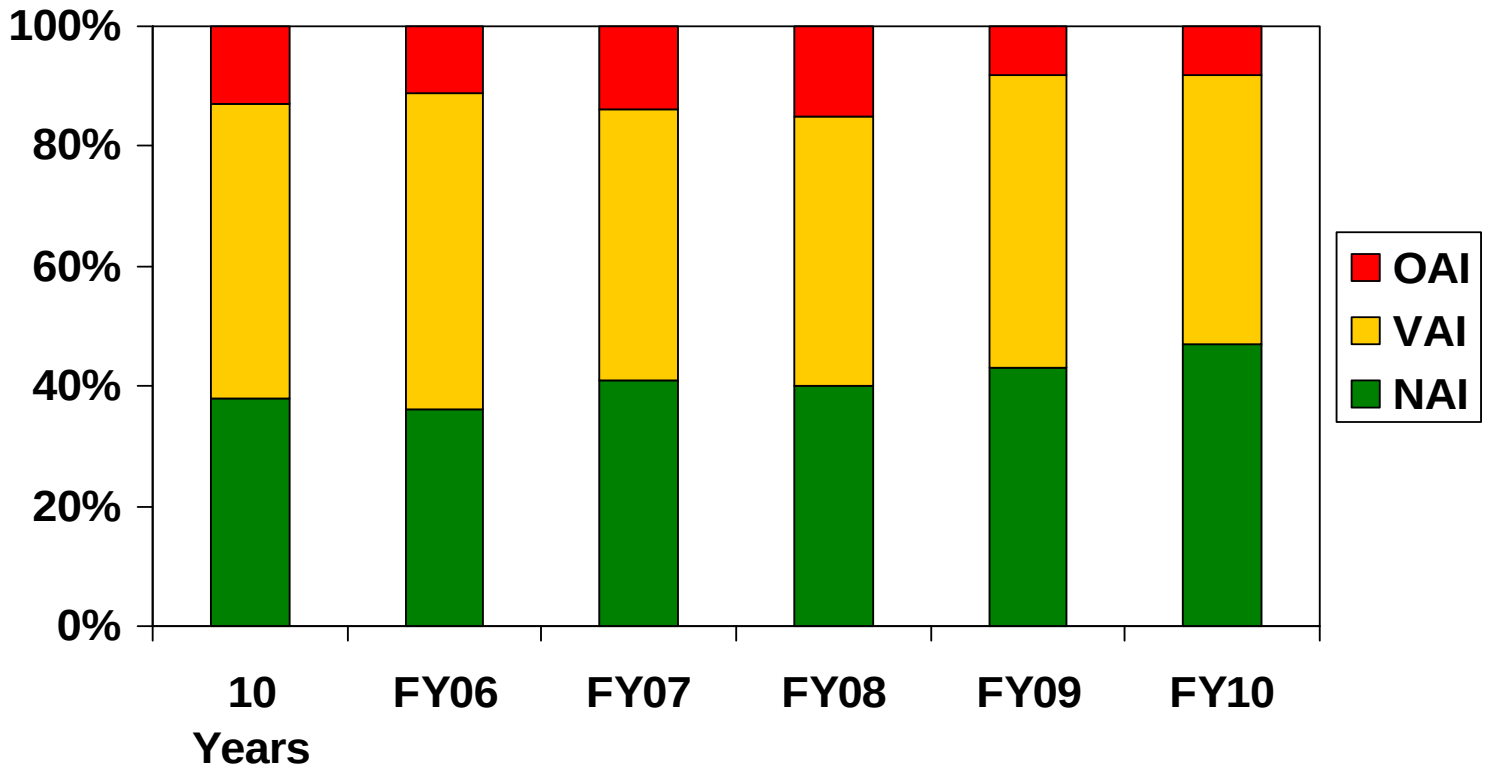
CDRH BIMO Inspections



CDRH BIMO INSPECTIONS
FY 2006 - 2010

Entity	2006	2007	2008	2009	2010
Sponsor	53	40	57	59	80
CI	200	183	155	163	218
IRB	59	92	88	79	81
GLP	24	8	1	4	7

CDRH BIMO Compliance Rates



FY10 Sponsor Deficiencies

- Not ensuring proper monitoring
- Inaccurate or incomplete correspondence
- Inadequate or no records of device shipment/disposition
- Not obtaining signed investigator agreement
- Not informing investigators
- Not securing investigator compliance
- Inadequate record retention
- Inadequate or no progress reports

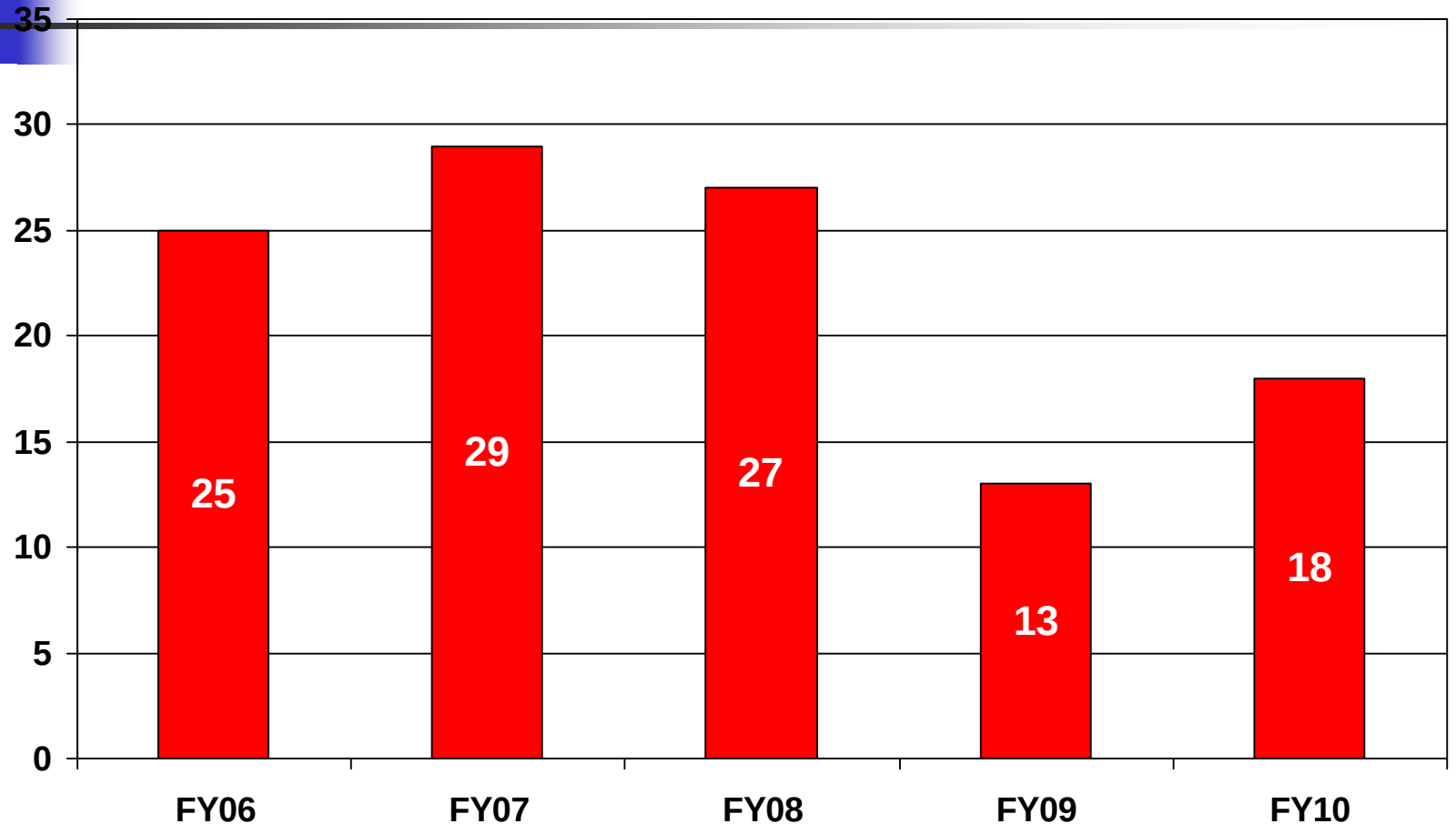
FY10 Investigator Deficiencies

- Not following investigational plan, FDA regulations, and signed investigator agreement
- Inadequate documentation of case history/device exposure
- Not properly obtaining informed consent
- Inadequate record of protocol and/or protocol deviations

FY10 IRB Deficiencies

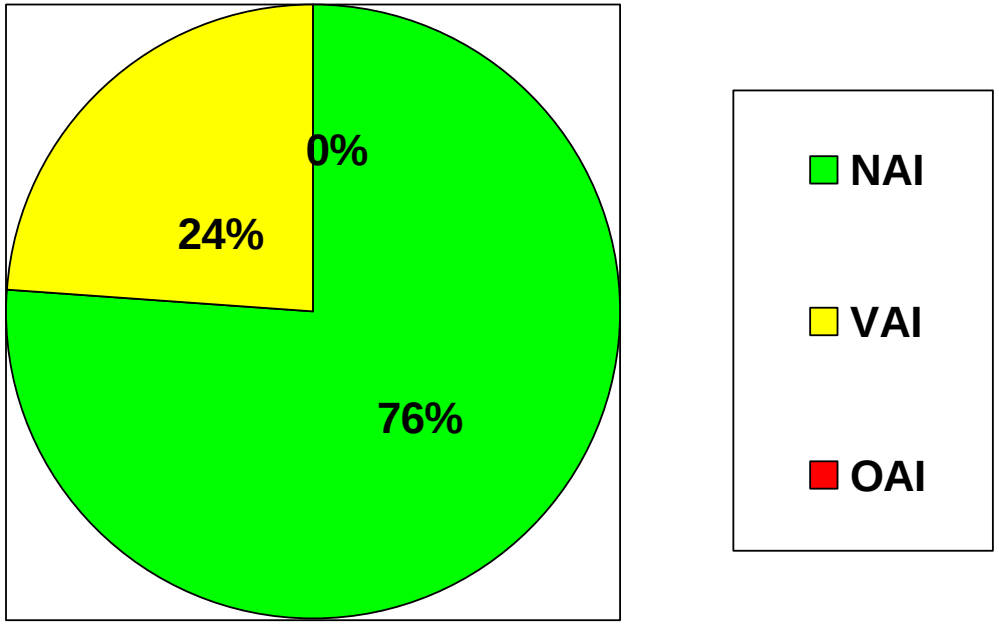
- Inadequate or incomplete minutes
- Inadequate initial or continuing review
- Inadequate or no membership roster
- Inadequate risk determination (SR vs NSR)
- Operating without a quorum
- Inadequate or no reporting of investigator non-compliance

CDRH BIMO Warning Letters



IVD BIMO Compliance Rate

FY10



FY10 IVD Sponsor Deficiencies

- Not ensuring proper monitoring
- Inadequate control of device

FY10 IVD CI Deficiencies

- Not following investigational plan, FDA regulations, and signed agreement
- Not obtaining informed consent
- Not ensuring control of devices
- Inadequate documentation of
  - receipt, use, and disposition of device,
  - case history/device exposure,
  - informed consent, and
  - protocol and deviations

IVD BIMO Regulatory Actions

FY10

- Warning Letters = 0
- Submissions withdrawn = 0
- Rejection of data = 0
- AIP = 0 new

*Multiple applications **remain** under AIP*

Getting off AIP

- Review & evaluate firm's internal review by outside consultant
- Review & evaluate Corrective Action Plan (CAP)
- **Determine CAP is adequate**
- Implement CAP
- Issue follow-up inspection
- Review & evaluate EIR

Tips for Success

- Follow good research/clinical practices
- Ensure studies are based on valid scientific evidence
- Monitor early and often
- Be responsive

Resources

- IVD Studies – Frequently Asked Questions

  http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf

- BIMO

  http://www.fda.gov/Training/CDRHLearn/ucm162015.htm#bimo

THANK YOU

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