Bioresearch Monitoring

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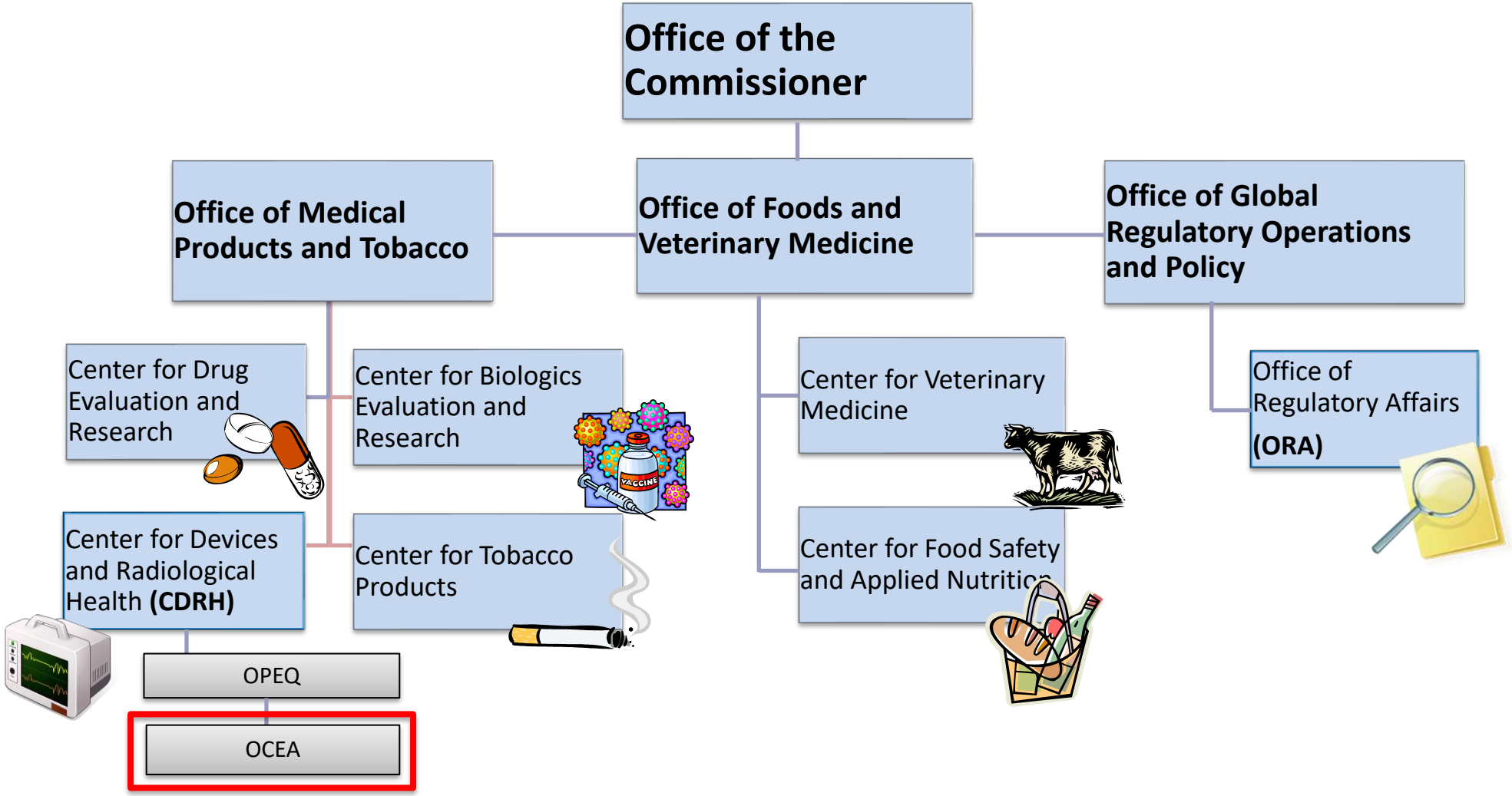
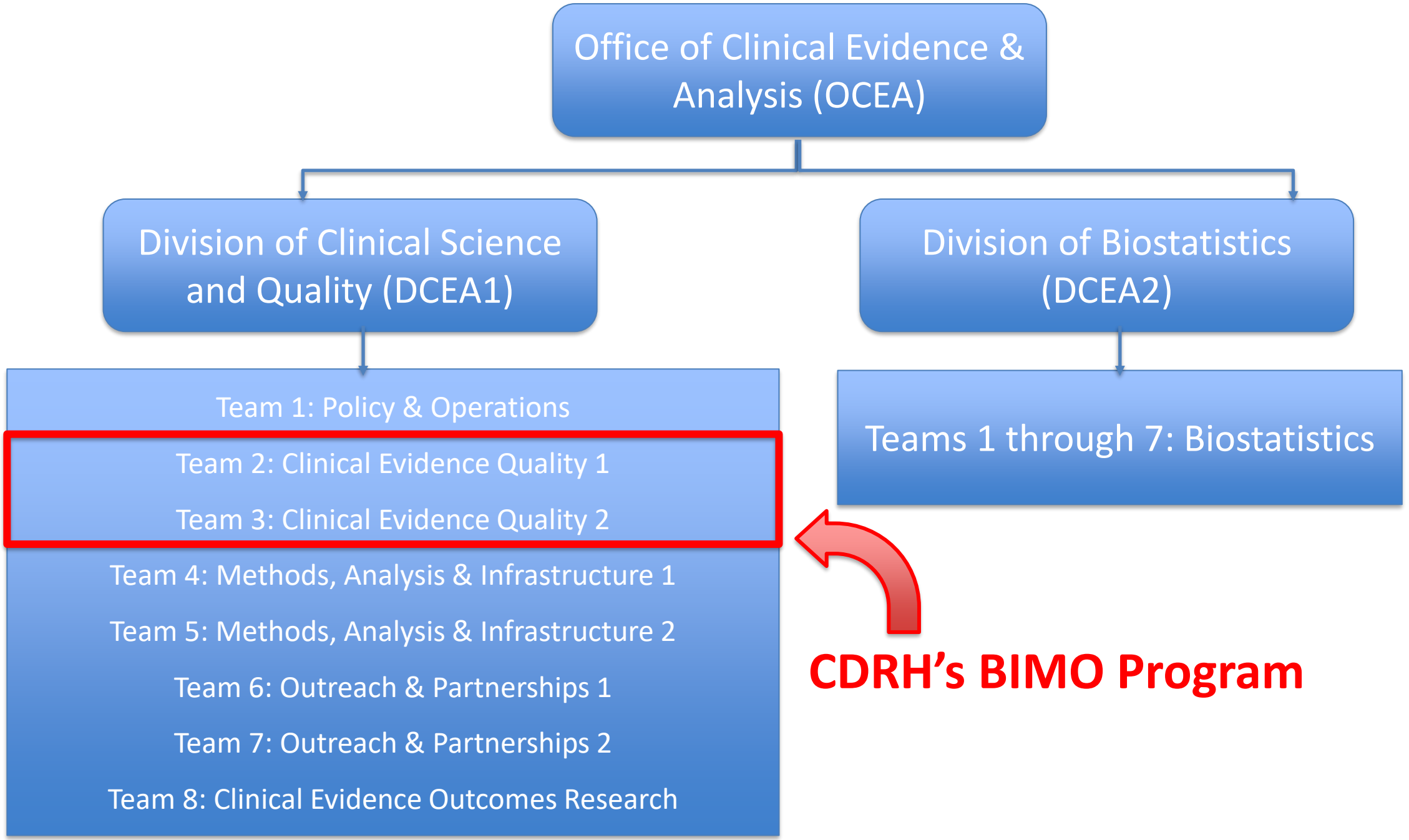
DCEA1: Division of Clinical Science and Quality
Office of Clinical Evidence & Analysis (OCEA)
Office of Product Evaluation and Quality (OPEQ)
CDRH

Outline

- BIMO Program
- Regulations
- Inspections & Data Audits
- Post-inspection Activities
- Challenges & Tips

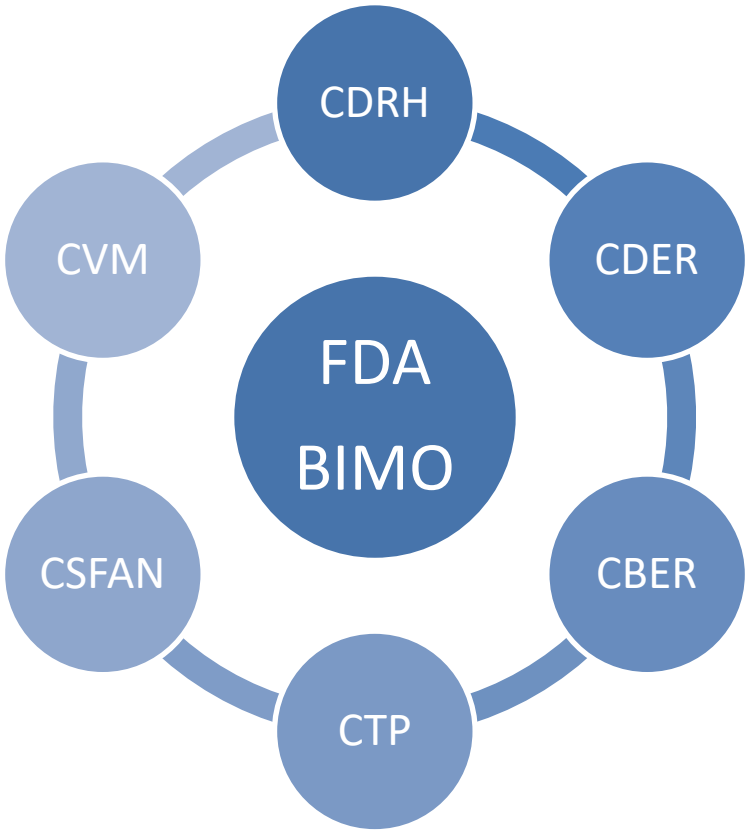
FDA Organization Chart




Office of Clinical Evidence & Analysis (OCEA)
Division of Clinical Science and Quality (DCEA1)
Division of Biostatistics (DCEA2)
Team 1: Policy & Operations
Team 2: Clinical Evidence Quality 1
Team 3: Clinical Evidence Quality 2
Team 4: Methods, Analysis & Infrastructure 1
Team 5: Methods, Analysis & Infrastructure 2
Team 6: Outreach & Partnerships 1
Team 7: Outreach & Partnerships 2
Team 8: Clinical Evidence Outcomes Research
Teams 1 through 7: Biostatistics
CDRH's BIMO Program

Bioresearch Monitoring (BIMO)

What is the BIMO Program?



What are its objectives?

- To protect the rights, safety, and welfare of human research subjects
- To verify the accuracy, reliability, and integrity of clinical and non-clinical trials data submitted to FDA
- To assess compliance with FDA's regulations governing the conduct of clinical and non-clinical trials, including those for informed consent and ethical review

FDA-wide Regulations

- **21 CFR Part 11:** Electronic Records
- **21 CFR Part 50:** Protection of Human Subjects
- **21 CFR Part 54:** Financial Disclosure
- **21 CFR Part 56:** Institutional Review Boards
- **21 CFR Part 58:** Good Laboratory Practice for Non-Clinical Laboratory Studies

Medical Device Specific Regulations

- **21 CFR Part 807:**

  Registration/Listing

  – Subpart E-Premarket Notification (510k)
- **21 CFR Part 809:**

  In Vitro Diagnostic Products (IVD)
- **21 CFR Part 812:**

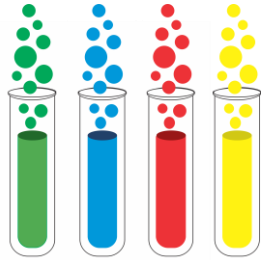
  Investigational Device Exemptions (IDE)
- **21 CFR Part 814:**

  Premarket Approval (PMA), Humanitarian Device Exemption (HDE)

21 CFR Part 812

- **Significant Risk (SR) studies**
  - Full requirements apply
- **Nonsignificant Risk (NSR) studies**
  - Abbreviated requirements – 812.2(b)
- **Exempt studies**
  - 812.2(c)(3) – Certain diagnostic devices per subparts (i – iv)
    - Parts 50, 56, and 809.10(c) apply
    - Do not represent device as safe & effective

Using Leftover Specimens



- Sponsor Responsibilities
  - Maintain written documentation
    - 7 Factors supporting use of leftover specimens
    - Specimen provider's policies and procedures to ensure that the subject **cannot** be identified
  - Provide documentation to IRB

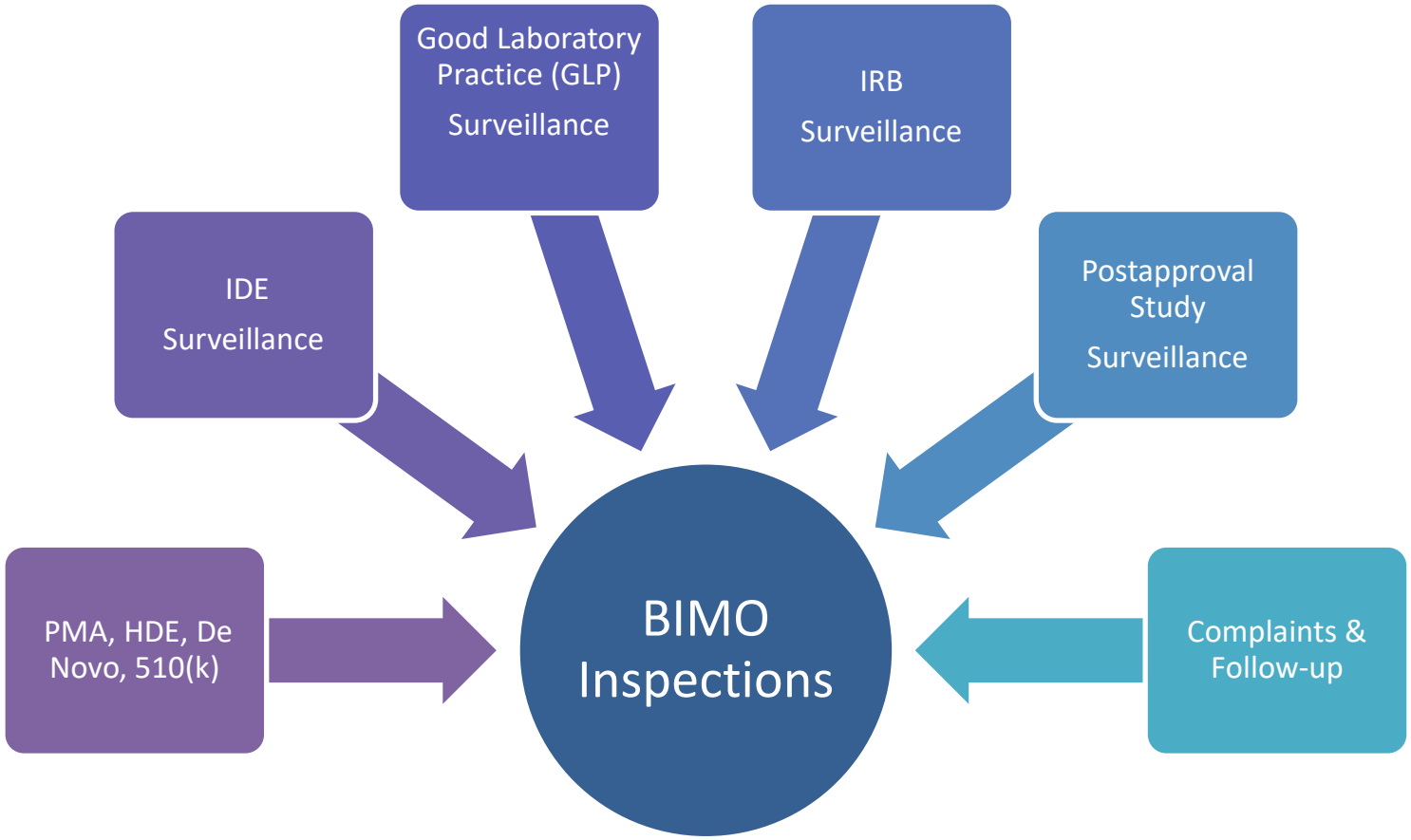
"Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable"

Entities Inspected

ORA's Office of Bioresearch Monitoring (OBIMO) inspects:

- Nonclinical Laboratories
- Institutional Review Boards (IRBs)
- Sponsors
- Contract Research Organizations (CROs) and Monitors
- Clinical Investigators (CI)
- Sponsor/Investigators (S/I)

Types of Inspections



Inspection Priorities

Top priority inspection assignments

Public health emergency (e.g., outbreak) ones

High priority inspection assignments

1) User fee driven and 2) For cause

Routine inspection assignments

Surveillance work, beginning of the Fiscal Year

Prior to Inspection

CDRH
- Select sites
- Send inspection assignment to OBIMO

OBIMO
- Call inspection site 3-5 days in advance to pre-announce (unless “For Cause”)

Site
- Prepare site staff & notify sponsor/monitor/IRB
- Ensure all required records are available

Inspection Conduct

- Issue “Notice of Inspection”
- Interview site personnel
- Review records
- Audit data
- Issue 483, if deviations from the regulations
- Discuss verbal observations, if any

Types of Records Reviewed

- Standard Operating Procedures
- Investigator agreements
- Correspondence between the Sponsor, IRB, CIs, FDA, etc.
- Monitoring logs
- Progress Reports (adverse events, protocol deviations...)
- Subject records (medical records, Case Report Forms (CRFs)...)
- Study Protocols & revisions
- Informed Consent versions
- Leftover Specimen documentation
- Hospital and laboratory records
- Radiological files
- Device accountability records
- Financial Disclosure Forms
- Data tabulations

Data Collection & Handling

- Any pertinent studies not included in FDA submission?
- Any CIs not included in FDA submission?
- Any subjects not included in the FDA submission?
- Data collection & handling procedures followed?

- Electronic records and data meet requirements?
- Any data transmission concerns?
- Original data entries and changes made by whom?
- Electronic data reviewed?

Data Quality & Reliability

- Protocol deviations?
- Investigator compliance issues?
- Inaccurate data? Changed data?
- Omissions of relevant data? *Intentionally* concealed?
- Untrue statements? *Intentionally* made?
- Pattern of errors?

Responding to Inspection Findings

- Present to FDA investigator any corrective actions taken and/or plans to prevent recurrence

- Respond in writing to FDA-483 within 15 days
  - Assess root cause and extent of the problem
  - Include corrective and preventive actions (CAPA)
  - Include projected timelines for implementation
  - Include supporting documentation (e.g., SOPs, training, etc.)

**Consider re-evaluating corrective/preventive actions in 6 months*

Post-Inspection

Site
- Submit response to 483 with corrective and preventive action plan, if applicable

OBIMO
- Complete an Establishment Inspection Report (EIR)
- Forward EIR & any 483 response for CDRH's review

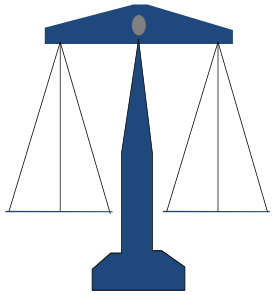
CDRH
- Review EIR and any supporting documentation
- Determine final classification
- Send post-inspection letter to site
- Communicate inspection findings to OHT

Compliance Classifications

- **No Action Indicated (NAI)**
  - No or minor objectionable conditions or practices
- **Voluntary Action Indicated (VAI)**
  - Objectionable conditions/practices
  - Isolated, low-risk, can be corrected easily
- **Official Action Indicated (OAI)**
  - Significant or egregious violations of regulations
  - Sanctions recommended

Compliance Tools

- **Regulatory Meeting**
- **Untitled Letter**
- **Warning Letter**
- Re-inspection
- Informal Conference
- Third Party Audits
- Rejection of Site Data
- Formal Adm. Hearing
- Disqualification
- Referral to Office of Human Research Protection (OHRP)
- Invoke Application Integrity Policy
- Civil Money Penalties
- Injunction
- Prosecution



Challenges…

- Missing or inadequate Informed Consent Form
- Lack of IRB Approval
- PMA referencing New Drug Application (NDA) for vital documents
- Device documents embedded in the NDA
- Missing study protocol for the investigational device
- Lack of data tabulations for device component of the clinical study
- Expedited timelines

Points to Consider

- Have a pre-submission meeting with CDRH
- Follow Good Clinical Practices
- Have written SOPs
- Secure agreements and financial disclosure from all involved parties
- Have a well-designed, detailed protocol
- Ensure trial personnel are qualified & trained
- Ensure IRB approval
- Ensure subjects are adequately informed
- Ensure changes and deviations are documented

BIMO Points of Contact

- Sheena Green – Assistant Director, CEQT 1&2
- Albert Rodriguez - Team Lead/Premarket Applications, CEQT 1&2

- CAPT Isatu Bah – IRB
- CAPT Martin Hamilton – IDE Early Intervention Program
- Irfan Khan – BIMO Operations & Outreach
- Stacey Priest – GLP
- Marisa White – Allegations of Research Misconduct

- BIMO Mailbox – BIMO-CDRH@fda.hhs.gov (*for* IRB concerns & Allegations)

Resources

- **CDRH Homepage**
  https://www.fda.gov/Medical-Devices

- **Bioresearch Monitoring**
  https://www.fda.gov/medical-devices/overview-device-regulation/bioresearch-monitoring

- **Bioresearch Monitoring Inspection Metrics**
  https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/bimo-inspection-metrics

- **IVD Studies – Frequently Asked Questions**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-diagnostic-ivd-device-studies-frequently-asked-questions

- **Guidance on Informed Consent – Using Leftover Specimens**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-informed-consent-vitro-diagnostic-device-studies-using-leftover-human-specimens-are-not

Resources (cont'd)

- **IDE Responsibilities**
  https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-responsibilities

- **Clinical Trial Registration**
  https://clinicaltrials.gov/ct2/manage-recs/fdaaa#WhoIsResponsibleForRegistering

- **Device Advice**
  https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance

- **Guidance Documents (Medical Devices and Radiation-Emitting Products)**
  https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products

Questions