Center For Veterinary Medicine (CVM) Bioresearch Monitoring (BIMO) Program

Presented by: Center for Veterinary Medicine (CVM)/
Office of New Animal Drug Evaluation (ONADE) & Office of Surveillance and Compliance (OSC)

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Supervisory Consumer Safety Officer,
BIMO and CGMP Branch

U.S. FOOD & DRUG ADMINISTRATION

New Supervisor for BIMO

- Where is Vernon Toelle ? Who am I?

- Vernon retired and I am now the supervisor for the CVM's BIMO and CGMPs Branch.

- Worked for FDA for 25 years, CVM 15 years. During that time, I supervised CVM drug program for over 10 years.

Recent Reorganization

- OS&C went through a reorganization in 2022.
- As a result, the Division of Compliance was split into two divisions:
- Division of Food Compliance
- Division of Drug Compliance

Recent Reorganization

- New structure of Division of Drug Compliance
  - Drug and Device – Veterinary Medical Support Branch
  - Drug and Device – Compliance Support Branch
  - BIMO and CGMP Branch

Recent Reorganization

- This reorganization allows resources and management to focus on detailed areas of animal drug and animal food programs.

- BIMO and CGMP branch can focus on the complete compliance drug process (beginning to end).

What is BIMO?

- Bioresearch Monitoring (BIMO) is a comprehensive Agency program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research
- CVM BIMO processes involve The Office of Surveillance & Compliance (OS&C) and The Office of New Animal Drug Evaluation (ONADE)
- BIMO and CGMP Branch leads the BIMO functions in OS&C
- The BIMO group is the “conduit/channel” between ONADE inspection requests and inspection execution by the Office of BIMO in the Office of Regulatory Affairs

Roles and Responsibilities

- ONADE
- BIMO and CGMP Branch
- ORA

CVM BIMO Inspection – Process planning

- Stage 1 – Pre-inspection

  initial interest in inspection – (ONADE & OS&C) → assignment submission to ORA

- Stage 2 – Inspection

  assignment submission to ORA → EIR returned to CVM

- Stage 3 – Post-inspection

  receipt of EIR in CVM → final classification and regulatory action

Our Goal

To develop a predictable, collaborative, and robust BIMO program that can provide needed assessments of the quality of research and the entities trusted in conducting this research used by drug sponsors and food additive manufacturers to support both new animal drug approvals and food additive petitions.

Stage 1 Highlights – Pre-inspection

- BIMO Coordinators – quality control check points
- Automated request form
- Defined timelines for the request and assignment development process
- Enhanced Assignment Memo and Inspection Package
  - Targeted to inspection goals

Stage 2 Highlights – Inspection

- Communicate with ORA and OBIMO inspection personnel
- Ad hoc meetings
- CVM Personnel BIMO Inspection Attendance

Stage 3 – Post-Inspection

- Once inspection is completed, the field investigator drafts the Establishment Inspection Report (EIR)
- The EIR is sent to OS&C BIMO for review and final inspection classification
- Inspections are closed out and decision on further regulatory action is determined (if needed)

Communicating Inspectional Feedback to Firms

- CVM's goal is to work with firms to ensure voluntary compliance.

- We have provided the FDA field with some internal guidance on providing firms with written feedback (C.I.)

- Form FDA 483 is a tool to provide firms with feedback on areas of improvement. The inspection is a snapshot in time.

Communication with Firms

- Our goal is to provide feedback so the firm can work toward voluntary compliance. In the past we may not have issued a Form FDA 483
- However, when the data was submitted to the review group there were concerns with the data which could end up being rejected.
- We hope by issuing written feedback, facilities understand our concerns and can work to correcting any deviations.

Final Thoughts

– We continue to develop and update the CVM BIMO Inspection process with a look to the future.

– We hope to work with industry to ensure we received quality data which would result in a quality approved products.

One CVM Animal Drug Review Lifecycle

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Stefanie R. Cook, RQAP-GLP, Quality Assurance Specialist & CVM BIMO Requests Coordinator, Quality Assurance Team
Amy-Lynn Hall, PhD, Biologist, Residue Chemistry Team
Hong Song, RQAP-GLP, Quality Assurance Specialist, Quality Assurance Team

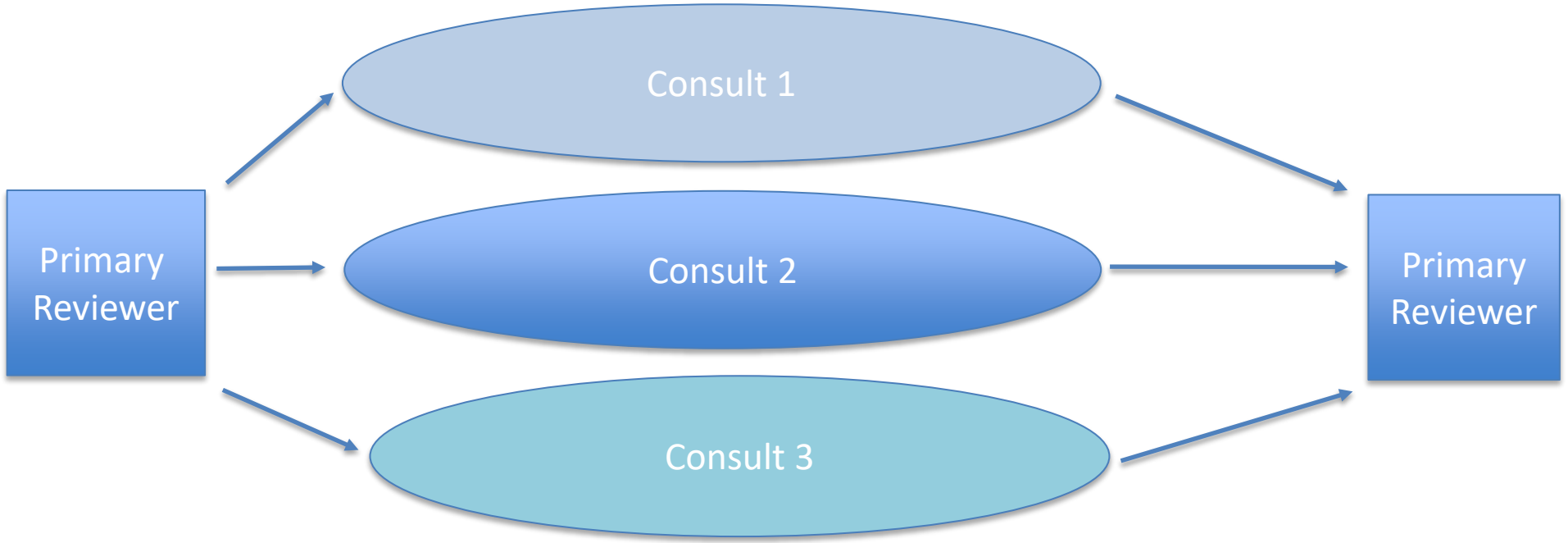
Objectives

- Overview of study review process (usually as part of a technical section)
  - Scientific reviewer and QASR perspectives
- How do we decide on a BIMO inspection / what leads to a BIMO inspection?
- Effect of BIMO Inspection observations on CVM's review

Study Reviewer Perspective

- Submission Assignment and sub consults (Members of the review team)
- Scientific Review Process
- Examples of issues that may warrant a BIMO request
- Effect of BIMO Inspection observations on CVM's review

Reviewer Perspective: Who looks at a study?



Reviewer Perspective: Conducting the Review

- Determine the purpose of the submission and review the various components of the submission
- Determine the need for consults/sub-consults
- Review the contents of the submission
  - Discuss with review team as needed
  - Amendments may be requested
- Make appropriate decisions regarding submission
- Issue CVM response letter

Reviewer Perspective: Considerations for Requesting a BIMO Inspection

- Reviewers evaluate a variety of factors including:
  - Overall study quality/data integrity
  - Gaps in study documentation
  - Date of last BIMO inspection
    - further evaluate other supporting documentation that were not submitted along with the study data.
    - assess compliance of the firms.
    - assess the impact of the issues on the reviewed study.

Reviewer Perspective – How to use the information from a BIMO Inspection

- Reviewers use information from the Establishment Inspection Report (EIR) to address gaps in documentation in the study submission and provide additional information on general facility or investigator quality.

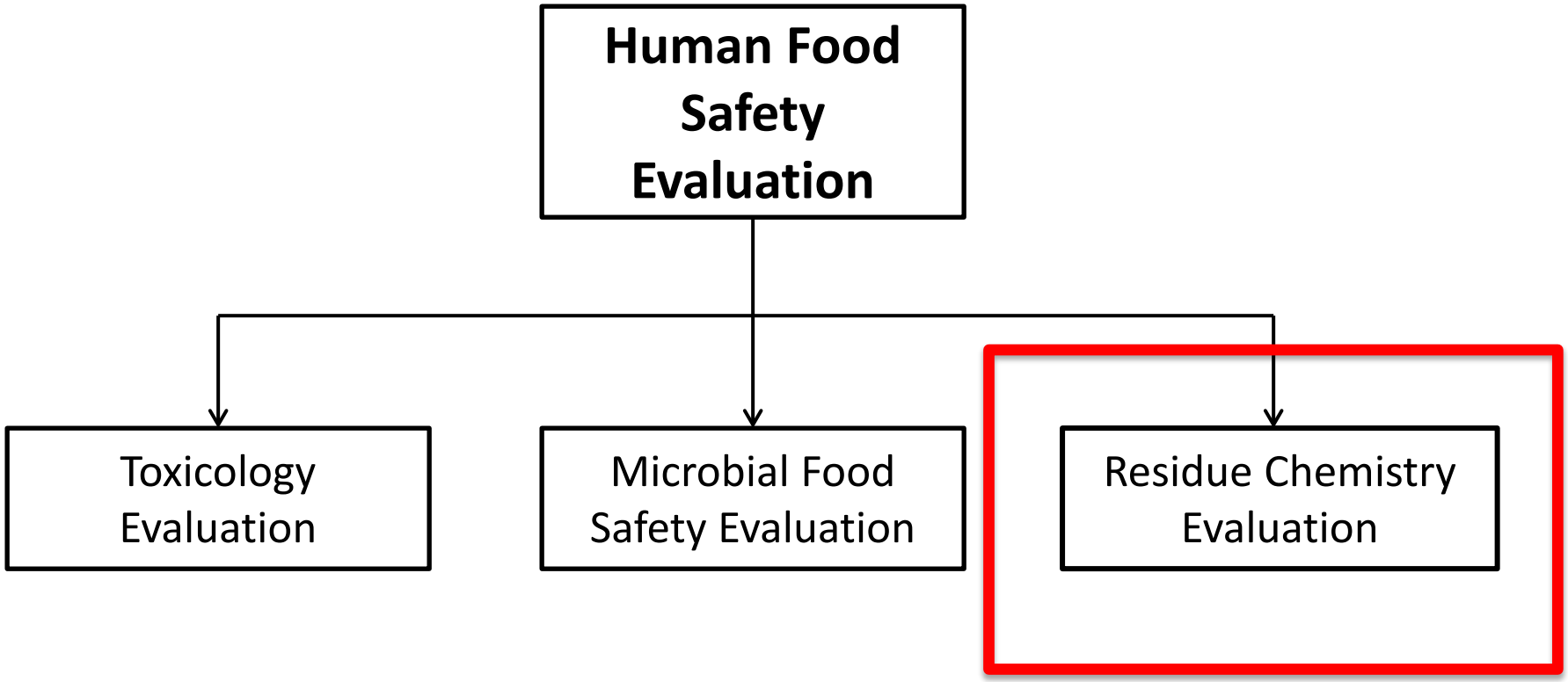
Reviewer Perspective

- Let's take a closer look at two types of reviewers conducting reviews of studies to support new animal drug applications.

SCIENTIFIC REVIEWER PERSPECTIVE

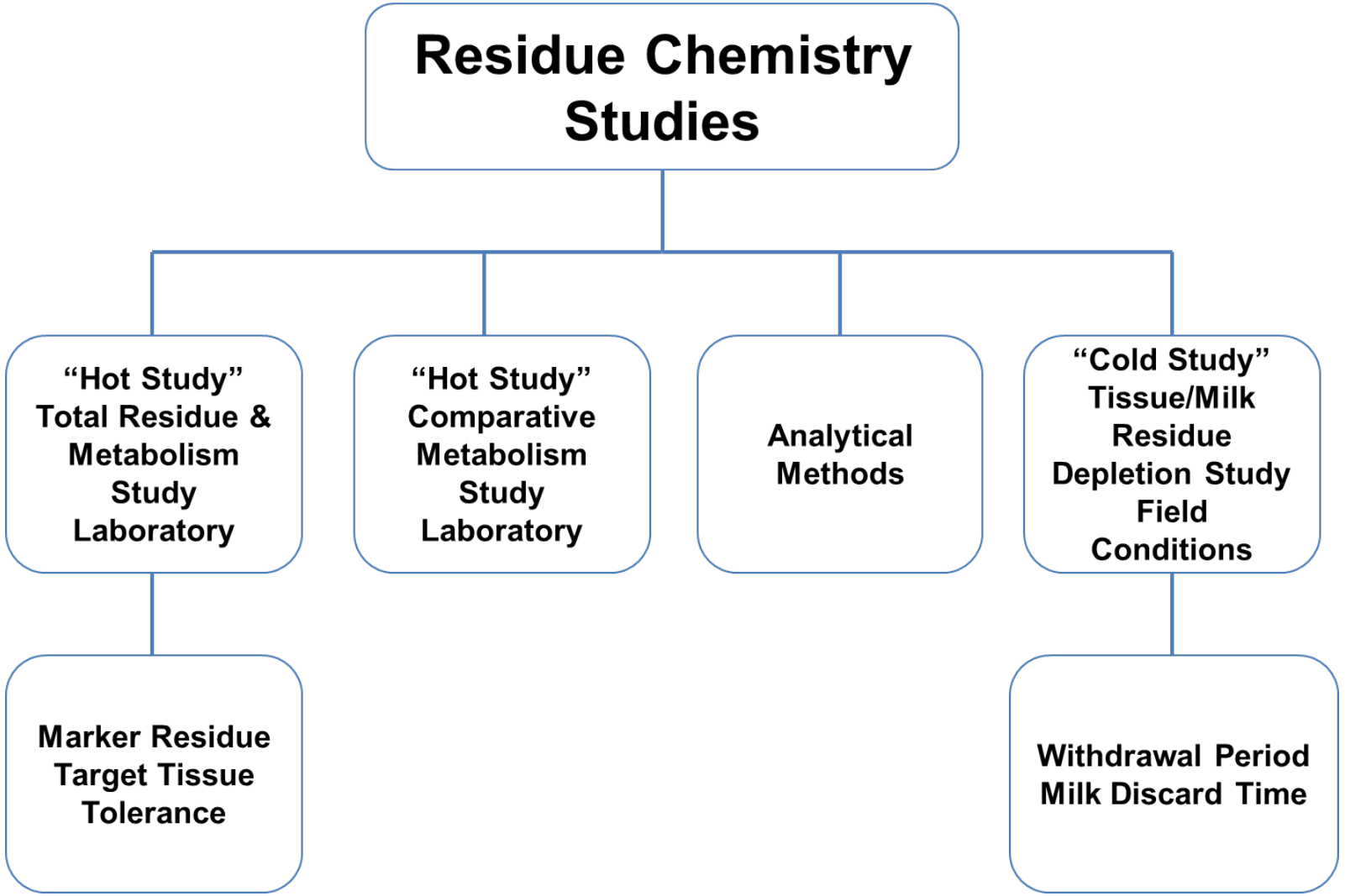
Human Food Safety Evaluation for Drugs Used in Food-Producing Animals

- Part of FDA's mission is to ensure food safety.
- Human food safety evaluation supports the approval of new animal drugs in food animals.
- We evaluate studies/information that assess the toxicity, microbial food safety, metabolic profile, and quantity of residues in edible products of animals treated with the proposed new animal drug.


Human Food Safety Evaluation
Toxicology Evaluation
Microbial Food Safety Evaluation
Residue Chemistry Evaluation

Residue Chemistry Evaluation

Control exposure to residues by assigning tolerances and withdrawal periods or milk discard times



Submission Assignment and Sub-Consults

- Submission assigned to primary residue chemistry reviewer (residue chemistry *vs.* analytical methods)
- May sub-consult to:
  - Other teams within the Division of Human Food Safety (Toxicology and Microbial Food Safety)
    - Determine status of those components
  - Quality Assurance Study Review (QASR)

Scientific Review Process

- Initial Triage of the Submission
  - Refuse to Review Screen
  - QASR submission screen, if applicable
- Run BIMO Selection Tool
  - Is BIMO request necessary?
- In-depth scientific review
  - Take into account any consulting reviews (toxicology, microbial food safety, QASR)

Issues That May Warrant a BIMO Inspection of a Residue Chemistry Study

- Evidence the study includes unhealthy animals
- Inadequate record of dose accountability
- Inadequate record of sample collection, initial sample preparation, storage of samples until analysis (freezer temperatures), shipment to lab, adequate temperature controls during shipment, method validation
- Inadequate record of adequate controls during analysis of samples
- Evidence of non-contemporaneous documentation of observations or deviations

Effect of BIMO Inspection Observations

- Helps to determine whether the inspected study or studies may be used in support of an animal drug application
  - Determine the impact of each cited issue on the integrity and acceptability of the study data
  - Take into account all scientific and data quality issues
  - Acceptance or rejection of study

QUALITY ASSURANCE STUDY REVIEWER PERSPECTIVE

Quality Assurance Study Reviewer (QASR) Evaluation for Drugs Used in Animals

- Quality Assurance Study Reviewers (QASRs) are experienced quality assurance professionals and experts in GLP/GCP
- QASRs receive consults to review safety (target animal safety and human food safety), bioequivalence, and effectiveness studies to evaluate the quality of study conduct
  - Standard of Conduct (GLP, GCP, etc.)
  - Protocol
- QASRs review documentation and data integrity
- QASRs communicate with the primary reviewer and review team regarding significant quality concerns identified in the study

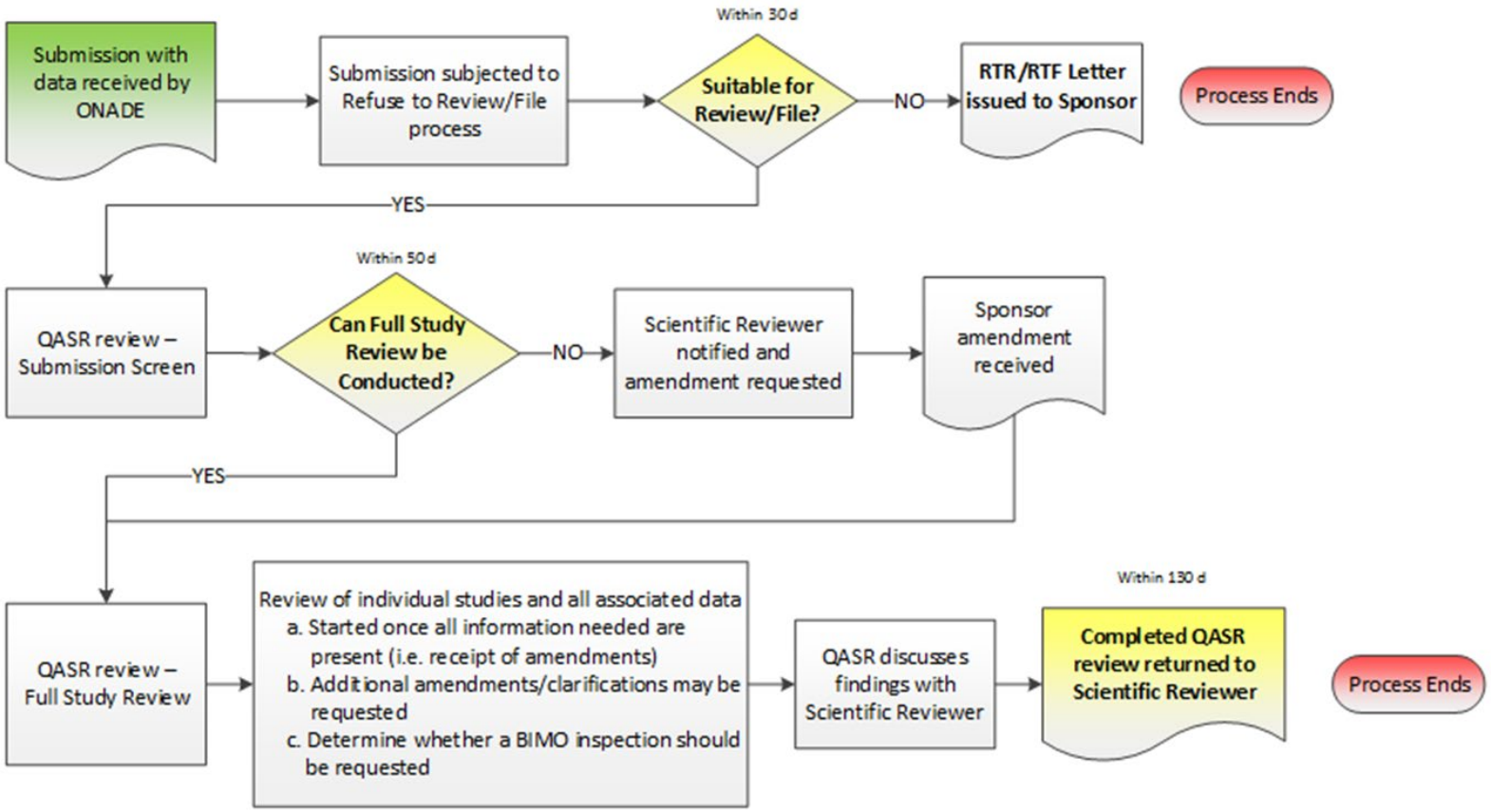
QASR Review Process

- QASR Review includes submission screen and full study review.
  - Submission Screen is a high-level review of the submission
    - to determine whether all applicable data and information necessary to conduct an in-depth study review are present, and
    - to identify any missing information that are required to complete the full study review
  - Full study review is a data quality assessment of all relevant aspects of each study provided in the submission
    - Five critical areas of focus
    - Final study report

QASR Review Process

- Critical areas of focus include but are not limited to:
  - Drug accountability
  - Dosage to animals
  - Animal accountability and enrollment
  - Study endpoints and critical variables
  - Adverse events and others

QASR Review Process – Workflow to Assess Quality



Issues That May Warrant a BIMO Inspection

- The quality of the data appears poor
- Significant gaps in documentation or inconsistencies in documentation
- Multiple significant protocol deviations
- The final study report does not accurately reflect the raw data
- Numerous and diffuse non-compliances
  - Study documentation does not meet principles of ALCOA (attributable, legible, contemporaneous, original, and accurate)
  - Study director and Investigator's responsibilities do not appear fulfilled as required per GLP or GCP

Effect of BIMO Inspection Observations

- BIMO Inspection observations address specific concerns about study conduct and data integrity
- BIMO Inspection observations provide additional information to the CVM review team as they determine the acceptability of a study to support a new animal drug approval.

Effect of BIMO Inspection Observations

- If a BIMO inspection was requested, QASR reviewer
  - Provides specific areas of focus for inspections.
  - Participates in the BIMO inspections when QA expertise is required.
- After the BIMO inspection is complete, QASR will review the following documents:
  - Firm's response to FDA 483 inspectional observations, if any;
  - Establishment Inspection Report (EIR);
  - Firm's response to the letters issued by CVM, when needed.

Effect of BIMO Inspection Observations

- If an FDA 483 is issued, QASRs often work with other members of the review team and the BIMO and cGMP Branch in the Office of Surveillance and Compliance to review the firm's responses to FDA 483 observations and letters to determine if those inspectional observations had significant impact on the integrity and acceptability of the study data.
- BIMO Inspections offer opportunities for CVM to better understand how entities are conducting their studies and where their gaps are in communication and understanding regarding high quality study conduct.

CVM's Role in the BIMO Inspection Process

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Renee Forde, PhD, RQAP-GLP, Biologist & CVM BIMO Inspections Coordinator, BIMO & CGMP Branch
Stefanie R. Cook, RQAP-GLP, Quality Assurance Specialist & CVM BIMO Requests Coordinator, Quality Assurance Team

Objectives

- Discuss overview of BIMO Inspection Process
- Highlight key offices and their roles
- Discuss BIMO request process
- Discuss BIMO inspection and EIR Review
- Discuss Inspection Classification & Closeout

CVM BIMO Inspection Process

Stage 1: Pre-inspection

BIMO Request → Assignment Memo

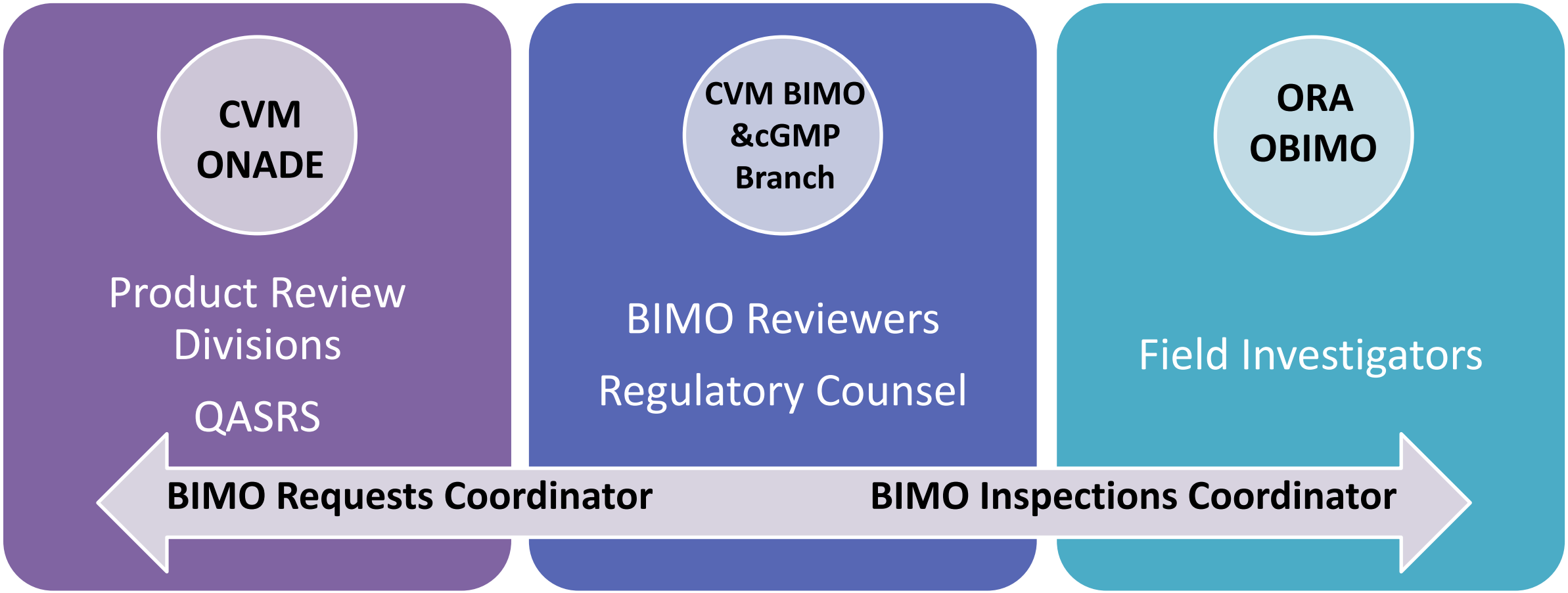
Stage 2 – Inspection

Inspection Planning & Execution → EIR submitted to CVM

Stage 3 – Post-inspection

Review EIR & Firm Response → Inspection Classification → Regulatory Feedback → Inspection Closed Out

Key Offices


CVM ONADE
Product Review Divisions
QASRS
CVM BIMO &cGMP Branch
BIMO Reviewers
Regulatory Counsel
ORA OBIMO
Field Investigators
BIMO Requests Coordinator
BIMO Inspections Coordinator

CVM BIMO Coordinators

BIMO experts with specific areas of focus

Two distinct and collaborative roles.

CVM BIMO Requests Coordinator

- Liaison and advocate for reviewers to ensure their inspectional goals are met

CVM BIMO Inspections Coordinator

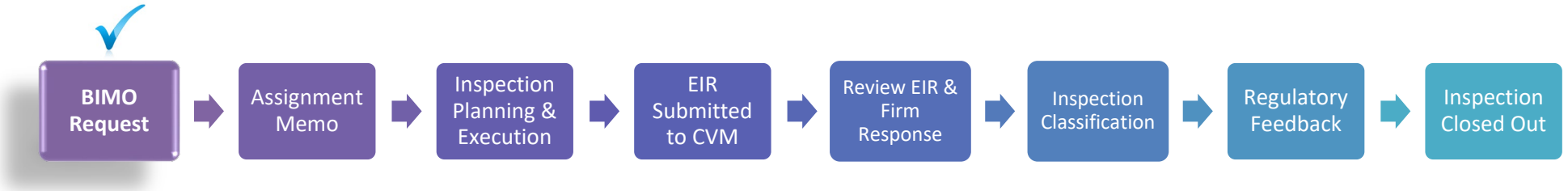
- Liaison and advocate for BIMO and compliance personnel

CVM BIMO Coordinators

- Track and monitor the BIMO inspection process from initiation to closeout
- Work to ensure communication, quality & predictability in CVM BIMO activities
- Monitor timeliness of actions
- Facilitate process improvement
- Collaborative relationship to ensure all parties get what they need in the inspection process
- Involved in CVM and agency-wide BIMO activities, and interact with industry on BIMO topics

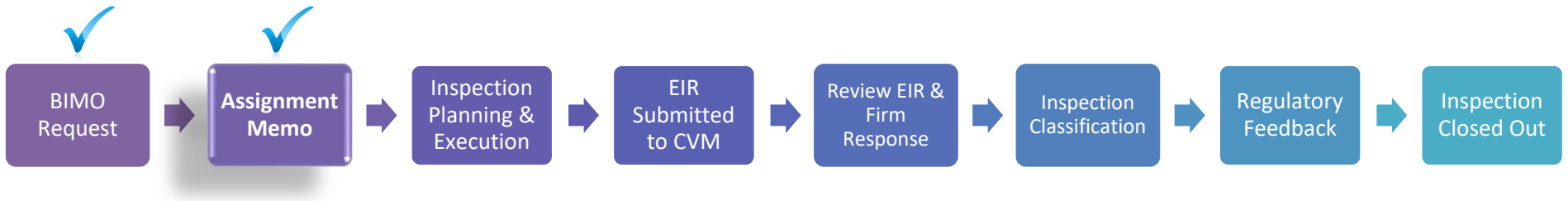
BIMO Inspection Request

- Developed by requesting review division to provide BIMO & cGMP Branch with information needed to develop assignment memo for ORA
- Goal is to provide the information ORA will need in order to conduct the inspection and provide adequate information to requesting review division
- May or may not include specific questions due to concerns noted by requesting review division
- Collaborative approach with CVM BIMO Coordinators

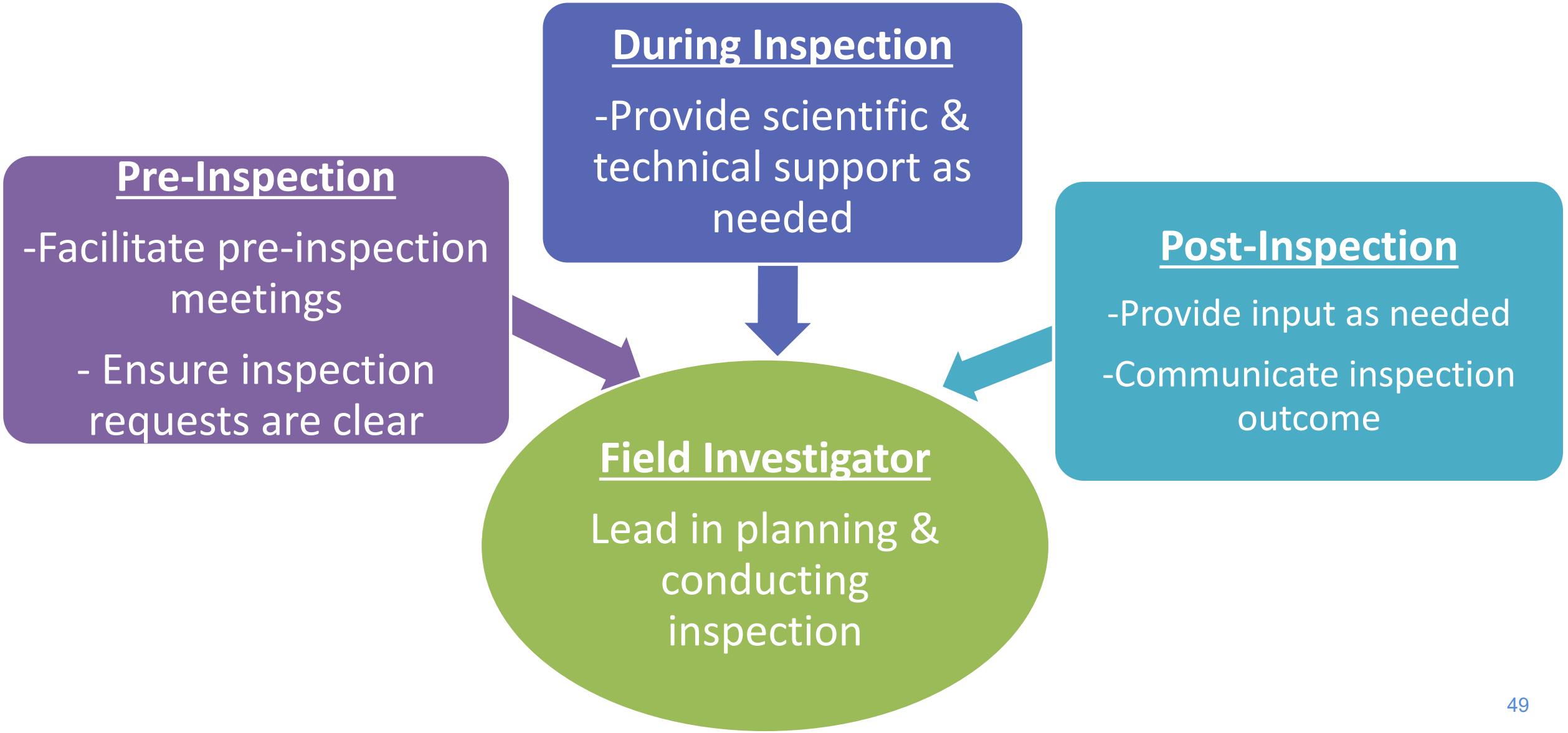


BIMO Inspection Assignment Memo

- Assignment Memo
  - Blueprint for conducting inspection- who, what, when, where, & why
  - Developed in the BIMO & cGMP Branch
  - Assignment Memo + Study related documents= Assignment Package
  - Submitted to ORA



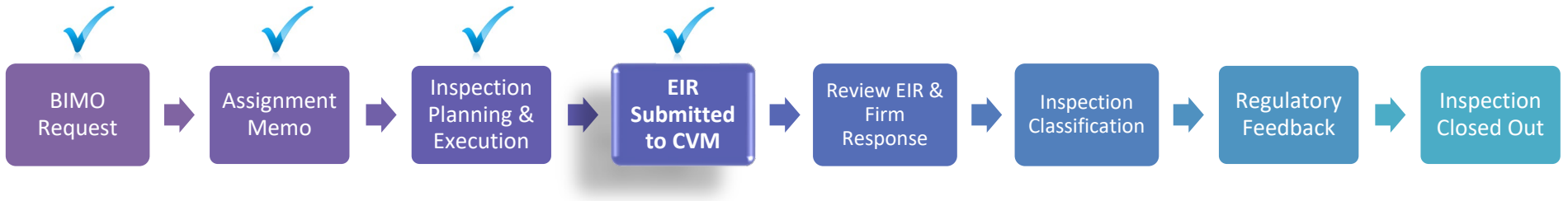
Inspection Planning & Execution



ORA EIR Review

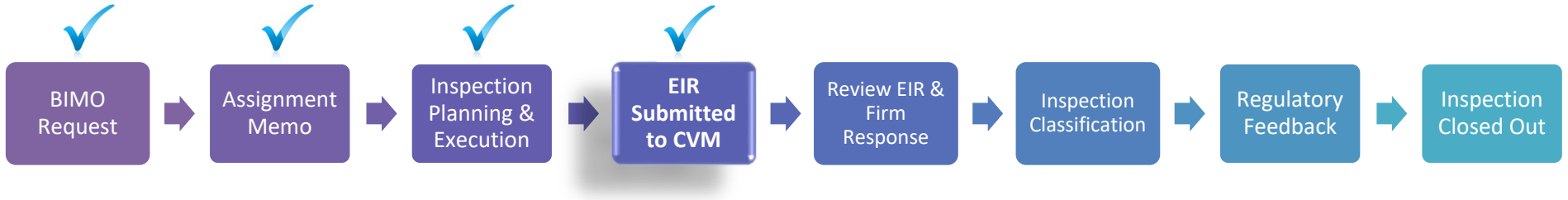
- EIR is written by the field investigator and undergoes a clearance process with ORA management
- The EIR is submitted to CVM
- The field investigator also provides an initial recommended classification for the inspection

CVM provides a final classification for the inspection



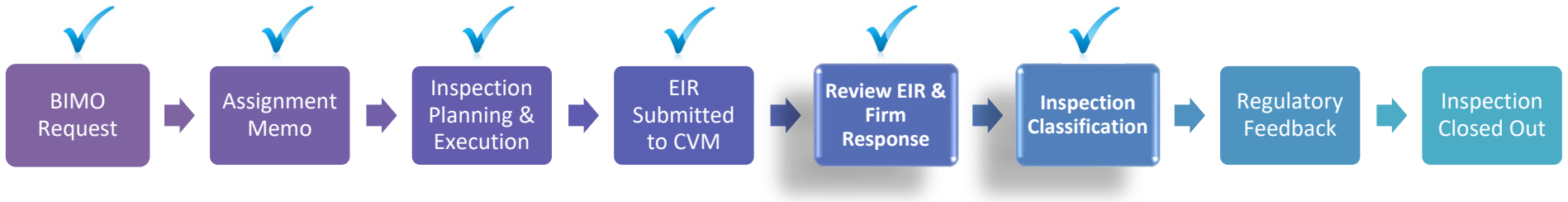
ONADE EIR Review

- EIR is distributed to relevant ONADE product review divisions for review and evaluation of the inspection results
- Purpose of ONADE review is to assess impact of observations on CVM's ability to use the inspected study in the regulatory decision-making process
- ONADE does not provide input on inspection classification or compliance regulatory actions



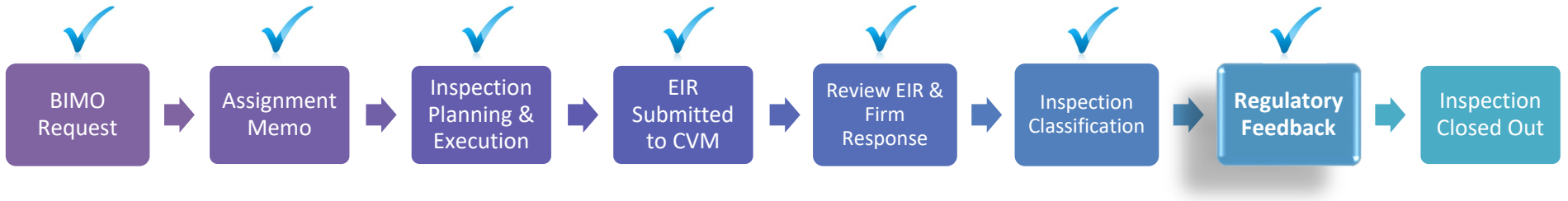
BIMO & cGMP Branch EIR Review & Classification

1. The final inspection classification and any subsequent compliance actions are based on the following:
   - EIR, exhibits, observations, inspection history
   - Form FDA 483 observations & firm's response (if applicable)
   - ONADE's EIR review
   - Regulatory Counsel input (if applicable)
2. Once established, BIMO & cGMP Branch communicates the final classification to ORA



Regulatory Feedback to Firms

No Action Indicated (NAI)	Voluntary Action Indicated (VAI)	Official Action Indicated (OAI)
• Copy of EIR • NAI Letter to Firm	• Copy of EIR • VAI Letter to Firm	• Untitled or Warning Letter



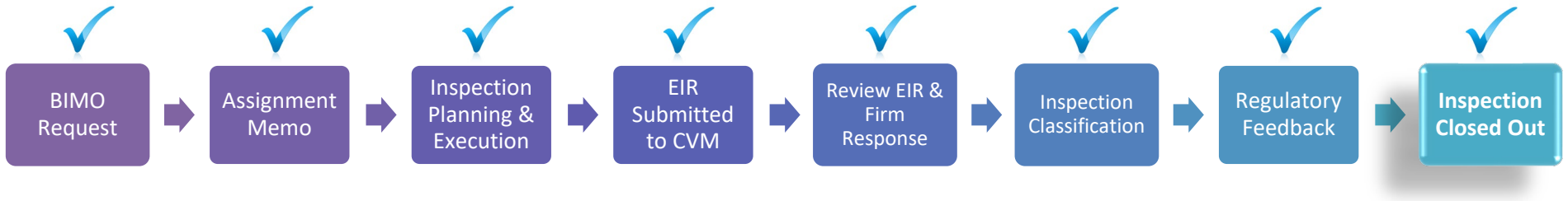
BIMO Inspection Closeout

CVM

- BIMO Inspection closed out when no further action is required
- CVM notifies ORA of final regulatory decisions and actions

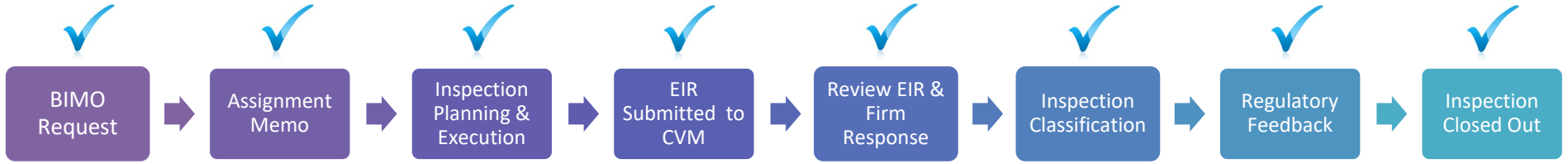
ORA

- Once the closeout notification is received, ORA will closeout the inspection in their system



Conclusion

- CVM and ORA work together to conduct a predictable, robust, and collaborative BIMO inspection program
- FDA would like to continue working with firms to achieve voluntary compliance and promote good study execution resulting in reliable study data that can support new animal drug approval
- The ultimate goal is to ensure that CVM uses high quality data to make their safety and effectiveness determinations when evaluating an unapproved new animal drug



Contact

- If you have questions about CVM/ONADE's data quality program, please contact the Quality Assurance Team Leader:

  Michelle.Kornele@fda.hhs.gov

- If you have questions about CVM's BIMO program, please contact the BIMO & cGMP Branch Chief:

  Dillard.Woody@fda.hhs.gov

Questions?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