How Does FDA Execute Pre-approval and Post-approval Inspections?

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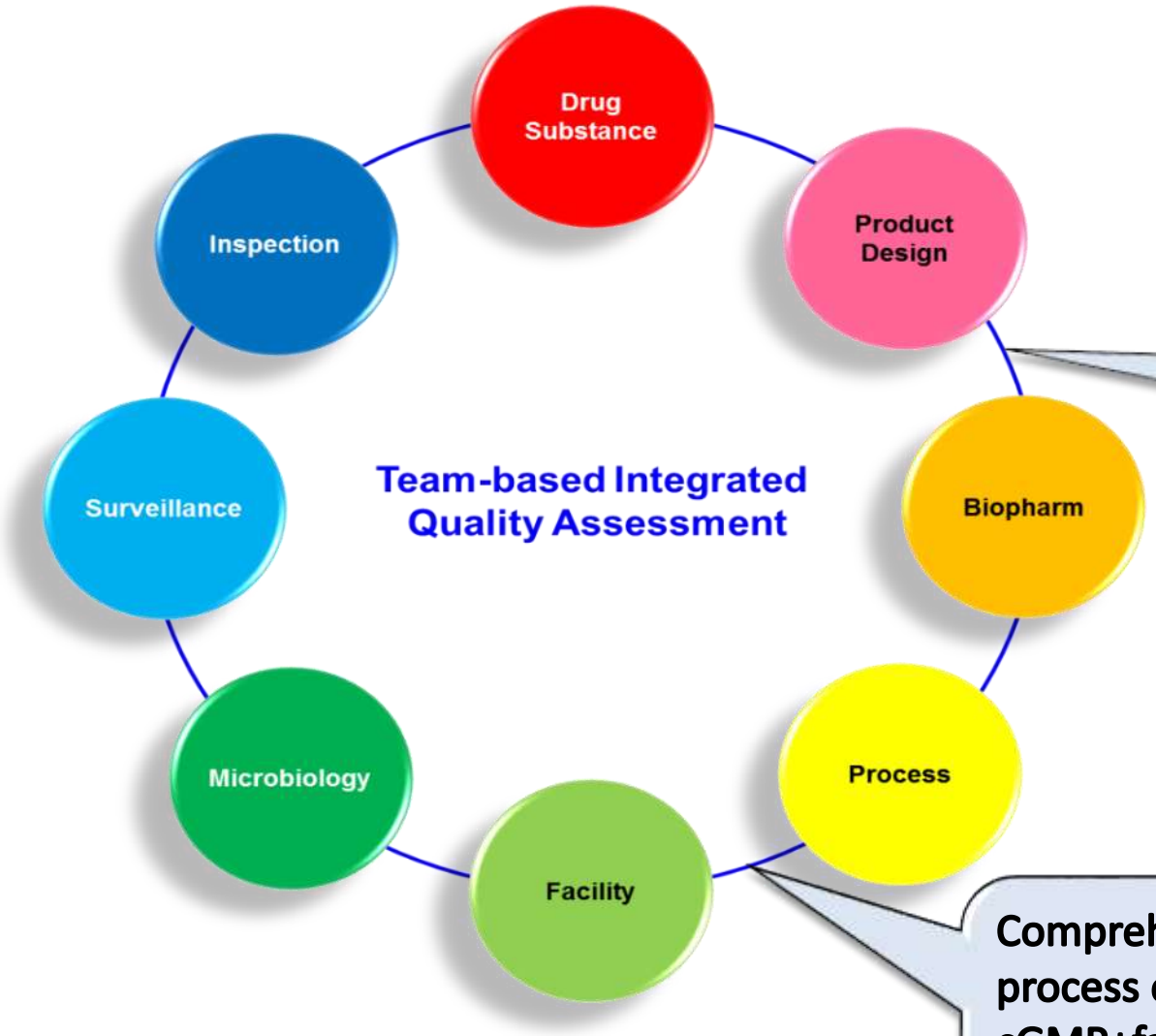
Learning Objective

- Understand FDA's decision making process for recommending pre-approval and post-approval inspections
- Understand how FDA executes these inspections in the field
- Learn some common pitfalls found at facilities

Outline

- Product specific inspections
  - Pre-approval inspection (PAI)
  - Post-approval inspection (PoAI)
- FDA-483 and citations
- Summary

Team-based Integrated Quality Assessment (IQA)



Inclusive of drug substance, drug product, manufacturing, and facilities, and maximizes each team member's expertise

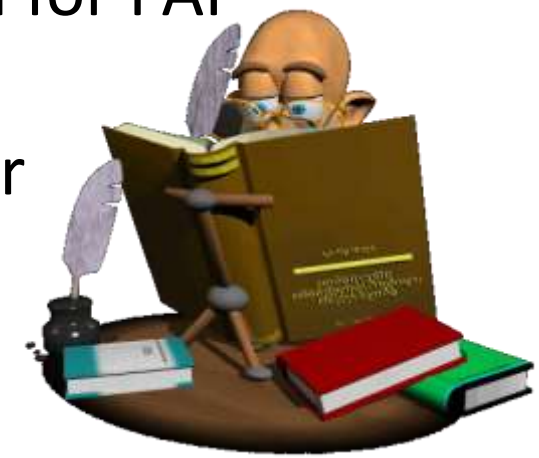
Comprehensive manufacturing process evaluation (process+ cGMP+facility capability) evaluations in conjuction with pre-/post-approval inspections

Common Issues: Pre-Inspection

- Inconsistencies between facility information in 356h form and Modules S.2 and P.3
- Identify firms not capable of manufacturing products
- Identify lack of conformance to application and data integrity issues:

Manufacturing Review communications

- Submission: Timely communication of Information Request (TCIR)
- Mid cycle review: Discipline Review Letter, Request for Additional Information for PAI
- Goal date: Action letter



Inspections

- **Pre-Approval:** Supports review & approval of marketing applications for drug products
- **Post approval:** Initiated after approval to verify that commercial-scale manufacturing and drug quality are per approved application
- Surveillance (Routine): Monitors the state of manufacturing quality to satisfy legal obligation to inspect production operations
- For Cause (Directed): Initiated in response to a specific event or observation; could result in recalls or enforcement actions

When to recommend a PAI?

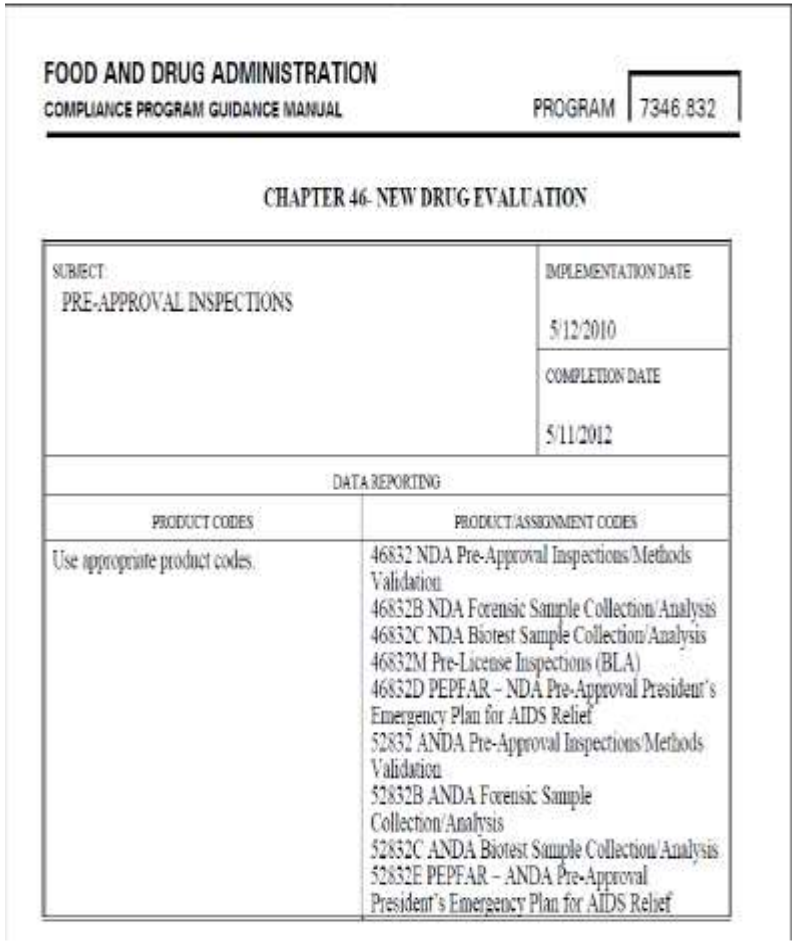
- Establishment is named for the first time
- First application filed by applicant
- New dosage form than previously approved at the product
- Substantially different or novel manufacturing process/design than previously approved
- Concerns about firm's quality systems
- Questions about the firm's capability of manufacturing quality products
- Scale-up concerns
- Product specific concerns
- NME, NTI, first generic?
- Time since last inspection?

Regulatory Considerations for PAIs

- Often limited or no commercial manufacturing experience at the time of PAI
- More focused on developmental data
- Emphasis on authenticity of data and application commitments
- Process validation plans
  - Stage 2b PPQ does not have to be complete at time of PAI or approval (A/NDA) however for sterile products, need to complete validation of sterility assurance.

PAI Program & workflow

- **All application types:**
  - -A/NDA, BLA, Treatment IND, Supplements
- **All manufacturing sites listed in the application**
- **Three primary objectives:**
  - -Objective 1: Readiness for Commercial Manufacturing
  - -Objective 2: Conformance to Application
  - -Objective 3: Data Integrity Audit



FOOD AND DRUG ADMINISTRATION

COMPLIANCE PROGRAM GUIDANCE MANUAL PROGRAM 7346.832

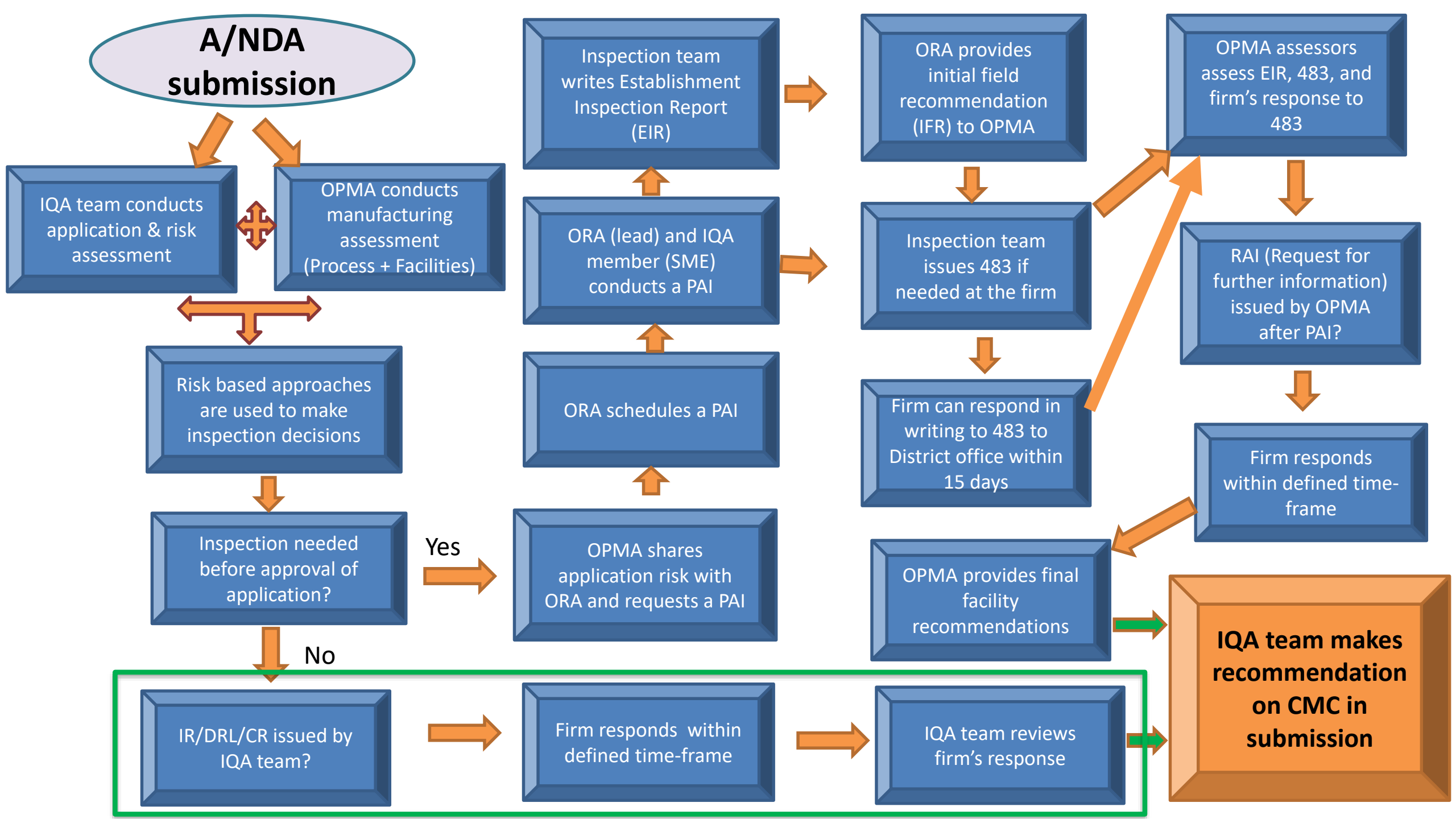
CHAPTER 46- NEW DRUG EVALUATION

SUBJECT: PRE-APPROVAL INSPECTIONS	IMPLEMENTATION DATE: 5/12/2010
	COMPLETION DATE: 5/11/2012

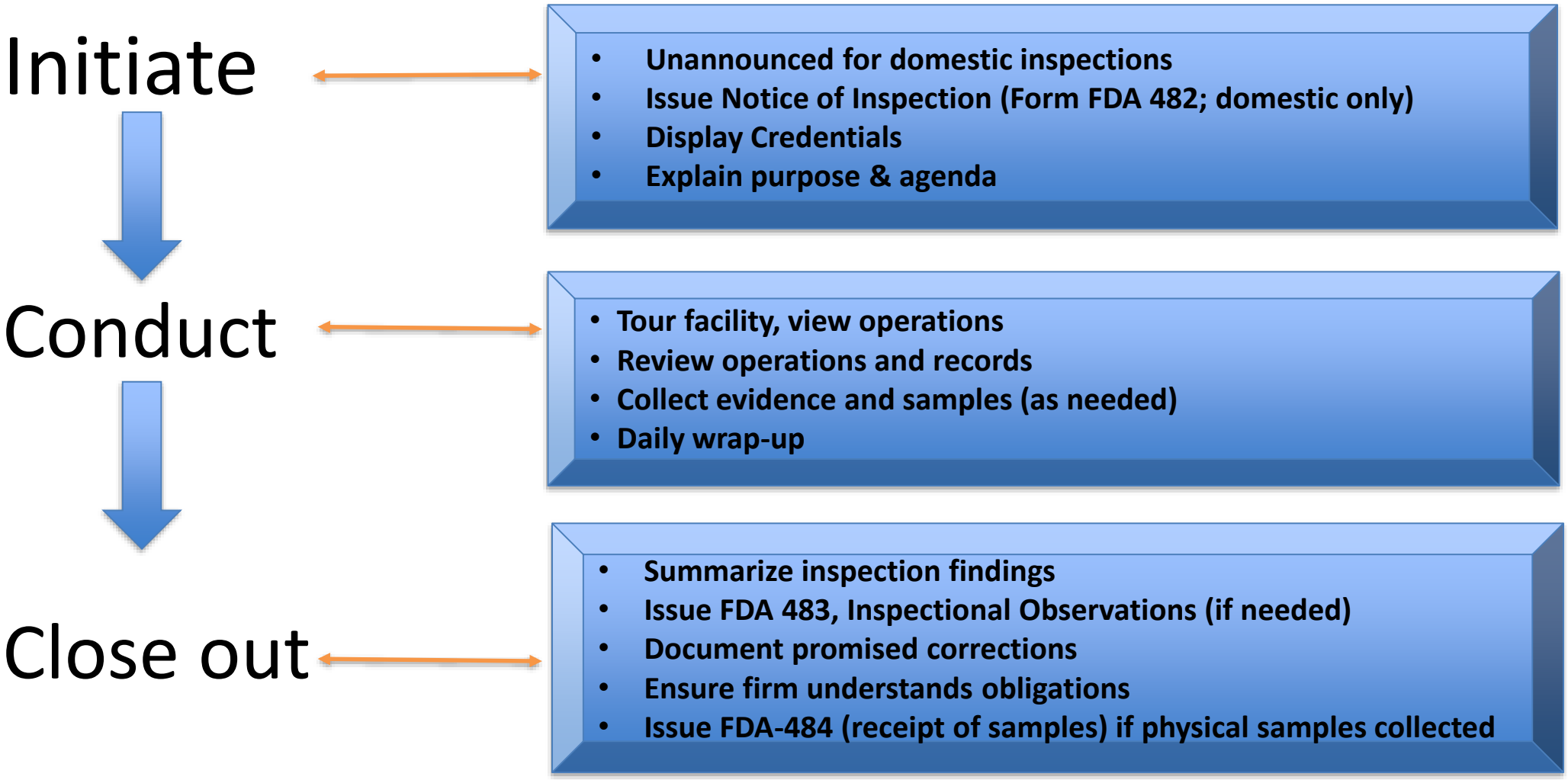
DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use appropriate product codes.	46832 NDA Pre-Approval Inspections/Methods Validation 46832B NDA Forensic Sample Collection/Analysis 46832C NDA Biotest Sample Collection/Analysis 46832M Pre-License Inspections (BLA) 46832D PEPFAR – NDA Pre-Approval President's Emergency Plan for AIDS Relief 52832 ANDA Pre-Approval Inspections/Methods Validation 52832B ANDA Forensic Sample Collection/Analysis 52832C ANDA Biotest Sample Collection/Analysis 52832E PEPFAR – ANDA Pre-Approval President's Emergency Plan for AIDS Relief

CP 7346.832


A/NDA submission
IQA team conducts application & risk assessment
OPMA conducts manufacturing assessment (Process + Facilities)
Risk based approaches are used to make inspection decisions
Inspection needed before approval of application?
Yes
No
OPMA shares application risk with ORA and requests a PAI
ORA schedules a PAI
ORA (lead) and IQA member (SME) conducts a PAI
Inspection team writes Establishment Inspection Report (EIR)
ORA provides initial field recommendation (IFR) to OPMA
Inspection team issues 483 if needed at the firm
Firm can respond in writing to 483 to District office within 15 days
OPMA assessors assess EIR, 483, and firm's response to 483
RAI (Request for further information) issued by OPMA after PAI?
Firm responds within defined time-frame
OPMA provides final facility recommendations
IR/DRL/CR issued by IQA team?
Firm responds within defined time-frame
IQA team reviews firm's response
IQA team makes recommendation on CMC in submission

Inspection at Facilities



Firms have the opportunity to respond to the Investigator's Observations or Discussion Points

- Verbal (during the inspection) and in writing (to the District Director)

15 days to respond for consideration of further action

Objective 1: Readiness for Commercial Manufacturing

Determine whether the establishment has a quality system designed to achieve sufficient control over the facility and commercial manufacturing operations

Objective 1a: Manufacturing & laboratory changes, investigations & trends

Objective 1b: Sampling, testing and evaluation of components, in-process materials, finished products, container closures.

Objective 1c: Facility & equipment controls to prevent cross-contamination.

Objective 1d: Change control, investigating failures/deviations, complaints/adverse events, conducting recalls, and reporting to FDA.

Objective 1e: Proposed commercial process & manufacturing batch record

Objective 2: Conformance to Application

Verify that the formulation, manufacturing or processing methods, and analytical methods are consistent with information contained in the CMC section of the application for the biobatch, proposed commercial batch, and API

This could also include:

- Observing processing and/or testing operations
- Examination of executed batch records, and when appropriate, comparison with the proposed commercial batch record.

Objective 3: Data Integrity Audit

Audit hardcopy and/or electronic *raw data* to authenticate the data submitted in the CMC section of the application

For example:

- Laboratory notebooks and associated chromatograms generated during release testing of executed batches
- Failure to include aberrant test results in CMC section
- Improper invalidation of OOS results

Useful Documents on a PAI

- **Product Development Report**
- **Batch Records**
- **Reprocessing/Reworking**
- **Process Validation**
  - Stage 1 – Process Design
  - Stage 2 – Process Qualification
  - Stage 3 – Continued Process Verification

PV link: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Applicant's Role

- The manufacturing & all associated facilities listed within the application
- Once an application is submitted to Center, all facilities should be considered **ready for inspection**.
- Make records available (as appropriate) to conduct the pre-approval inspection
- Ensure facility is cGMP compliant and ready for an FDA inspection

Inspection Team's Role

- Conduct PAI

Assess the following:

- Quality Systems
- Manufacturing Operations
- Sampling Plans
- Laboratory

- Inform firm management at the conclusion of the inspection of his/her recommendation to PAM (VAI/NAI/OAI). Issues FDA 483, as appropriate

Post-Approval Inspection (PoAI) & workflow

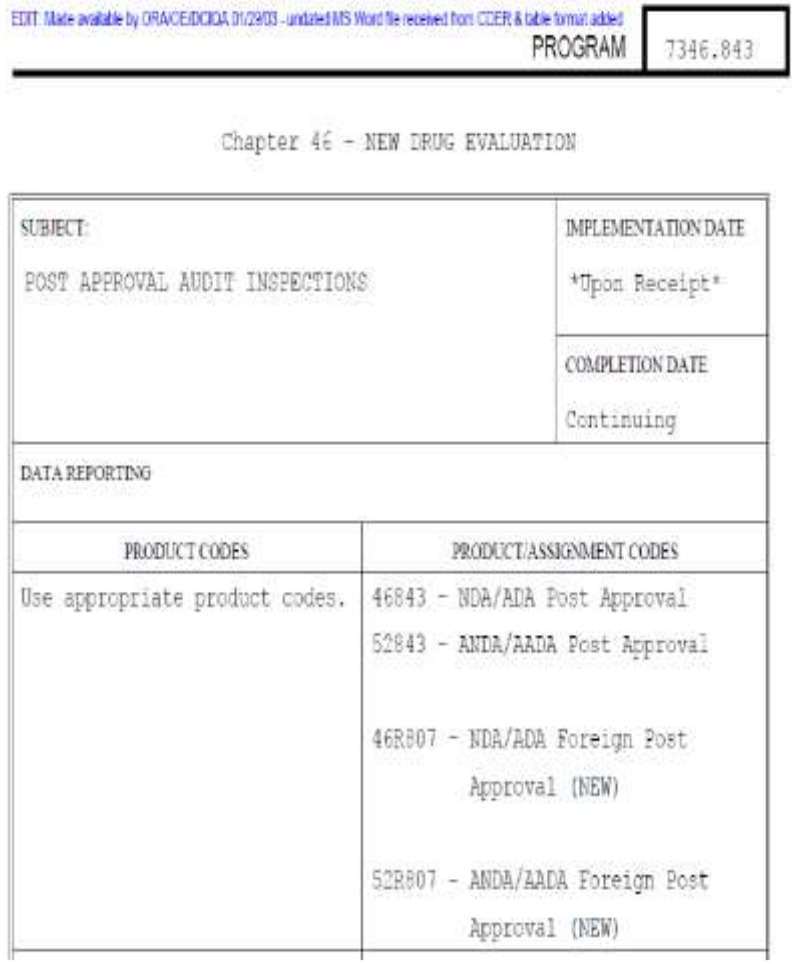
- Post-market Inspection cycle
- Conducted within certain time frame of application approval
- Based on product/process/facility risk profile

- Focuses on the *process validation lifecycle* & *manufacturing changes* following approval; post-approval "commitments"

- Changes in perceived risk may also initiate a PoAI

- Ensures *commercial-scale processes* for an approved product conform to application commitments and CGMP requirements

- The inspection information is used to *update lifecycle risks* for a product or to determine any regulatory actions.



EDIT: Made available by ORA/CE/DCIDA 01/23/03 - updated MS Word file received from CDER & table format added

PROGRAM 7346.843

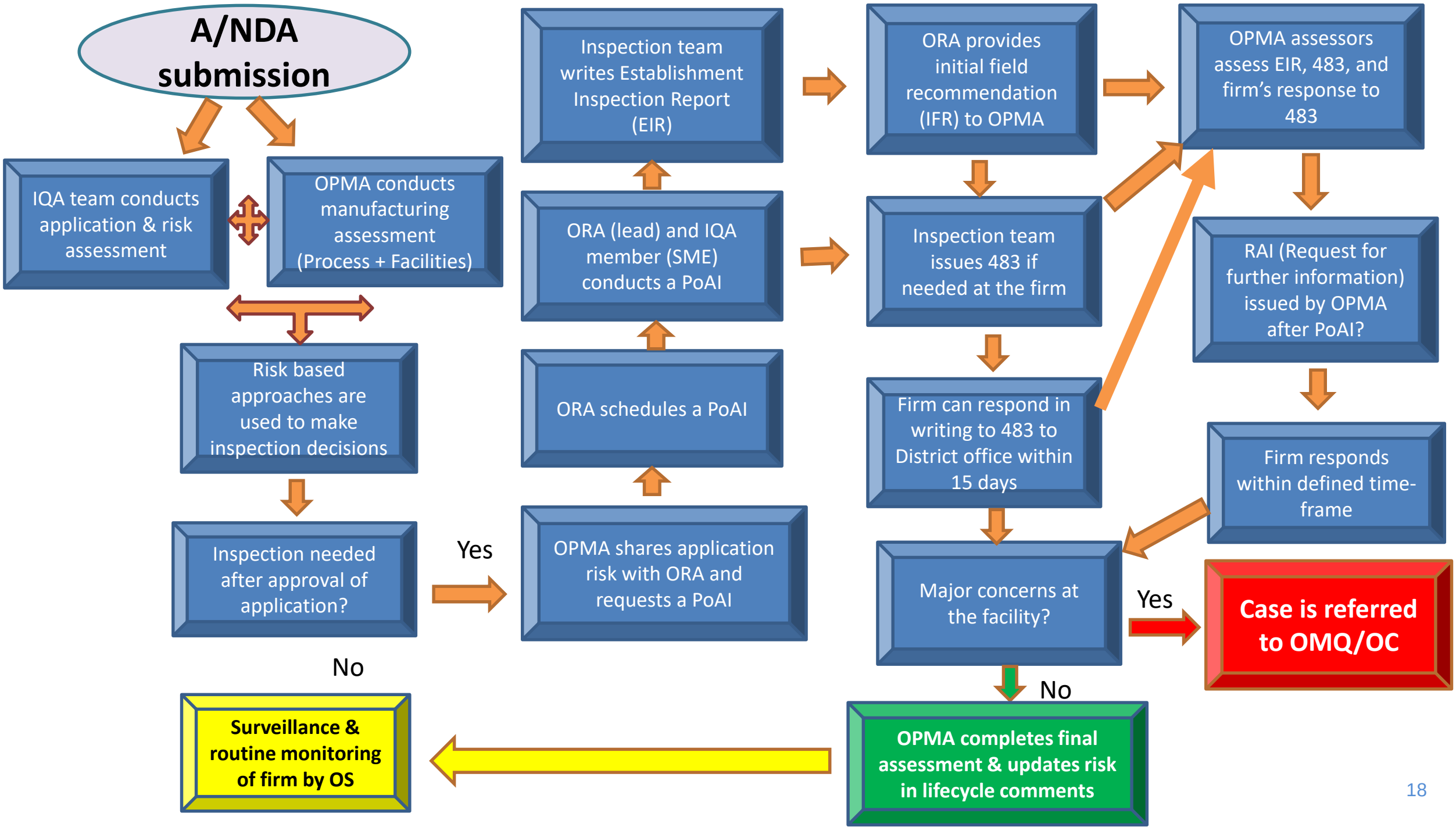
Chapter 46 - NEW DRUG EVALUATION

SUBJECT: POST APPROVAL AUDIT INSPECTIONS	IMPLEMENTATION DATE: *Upon Receipt*
	COMPLETION DATE: Continuing

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use appropriate product codes.	46843 - NDA/ADA Post Approval 52843 - ANDA/AADA Post Approval 46R807 - NDA/ADA Foreign Post Approval (NEW) 52R807 - ANDA/AADA Foreign Post Approval (NEW)

CPGM 7346.843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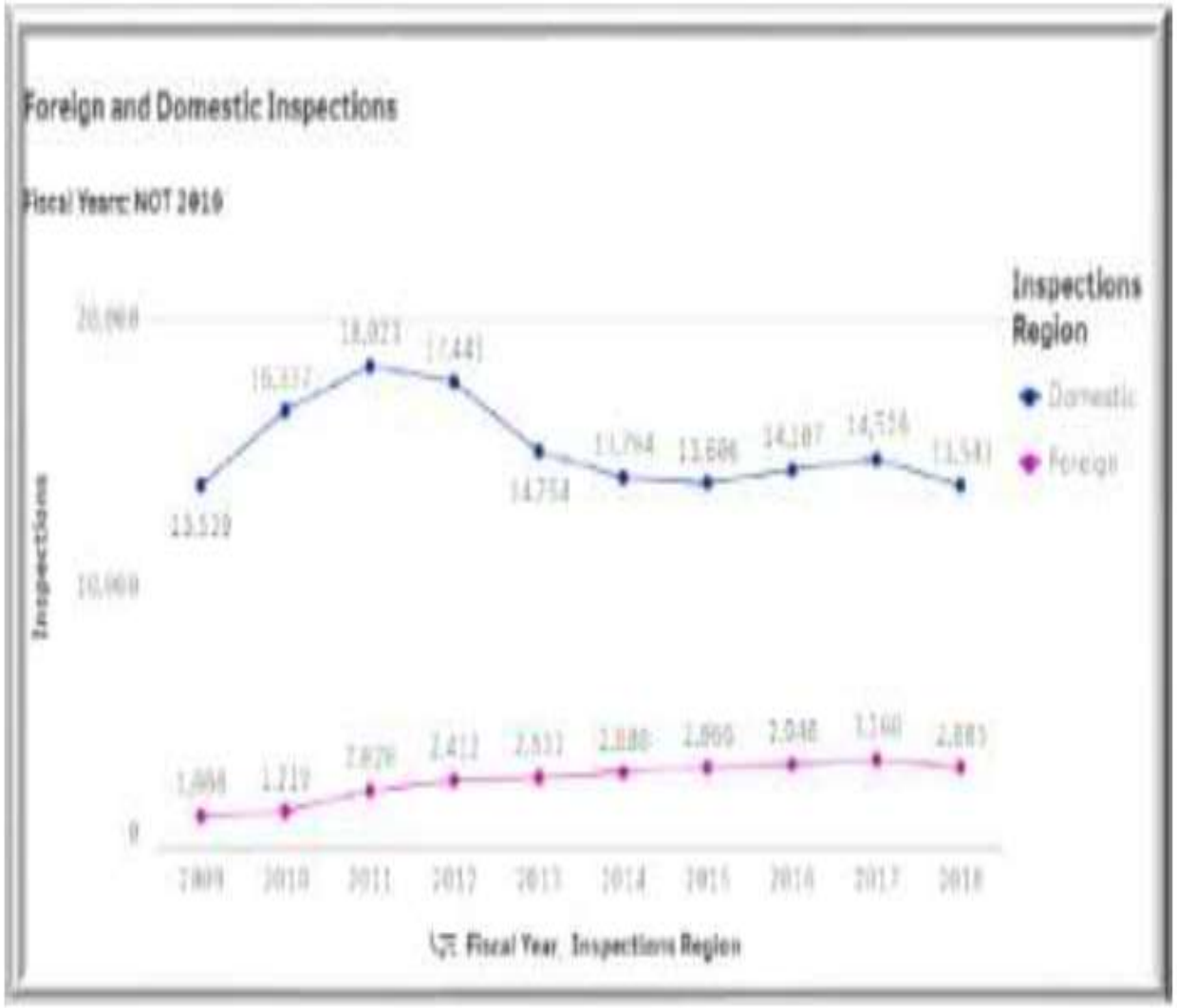
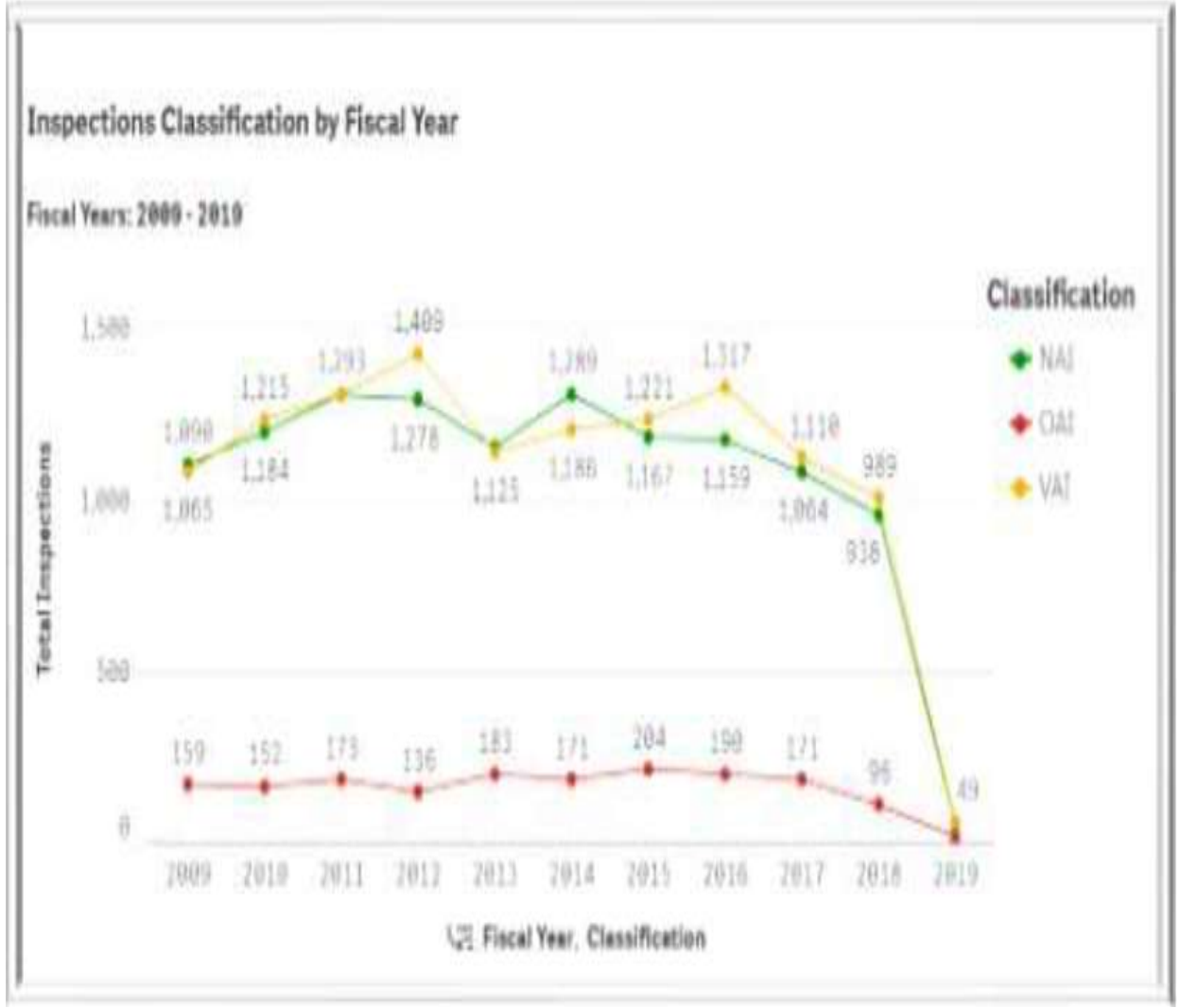
Inspection team writes Establishment Inspection Report (EIR)
ORA provides initial field recommendation (IFR) to OPMA
Inspection team issues 483 if needed at the firm
Firm can respond in writing to 483 to District office within 15 days
Major concerns at the facility?
Yes
Case is referred to OMQ/OC
No
OPMA completes final assessment & updates risk in lifecycle comments
Surveillance & routine monitoring of firm by OS
OPMA assessors assess EIR, 483, and firm's response to 483
RAI (Request for further information) issued by OPMA after PoAI?
Firm responds within defined time-frame

Inspection outcomes: historical Trends

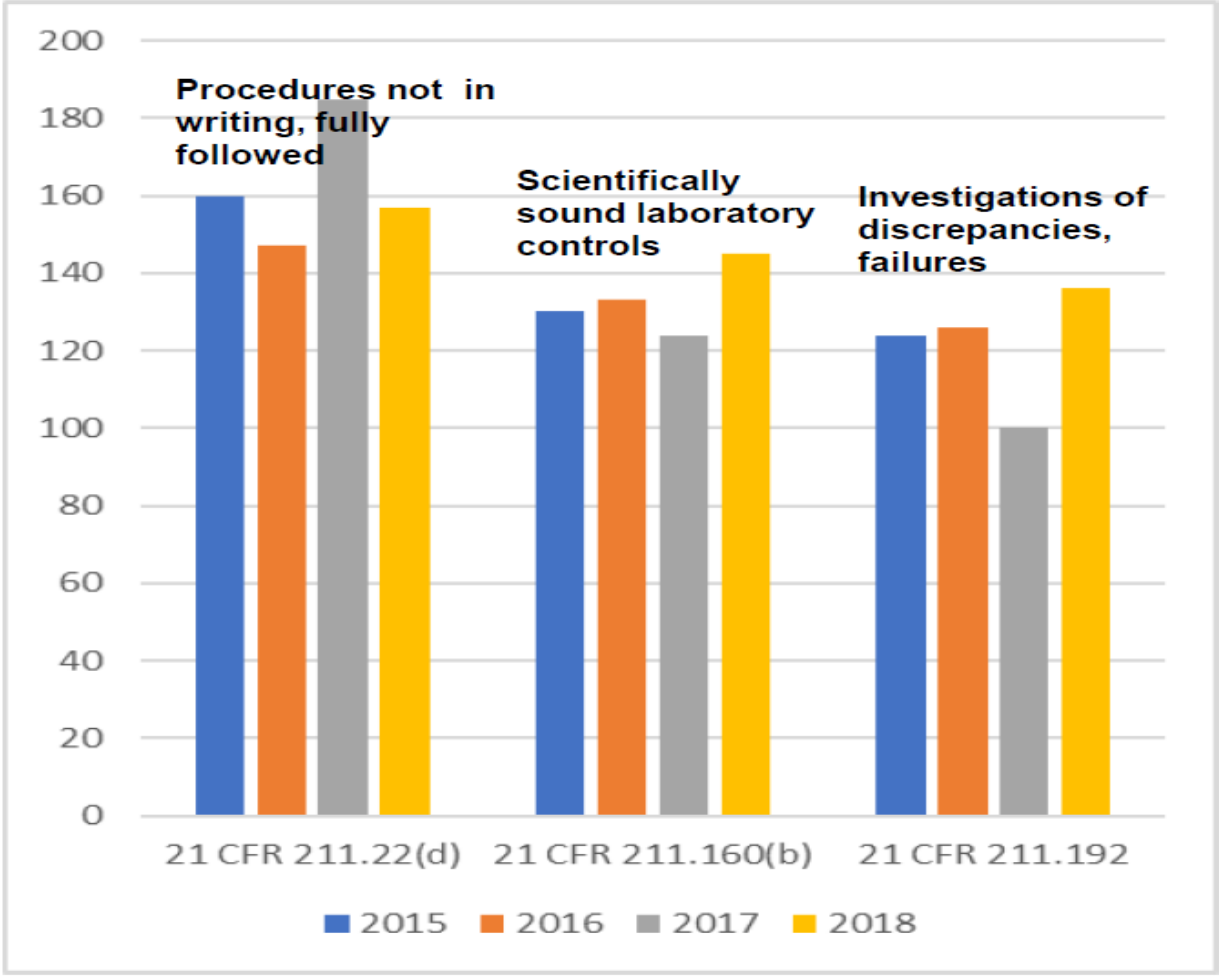




FDA-483: Top 3 Citations

Inadequate Quality Unit oversight of -

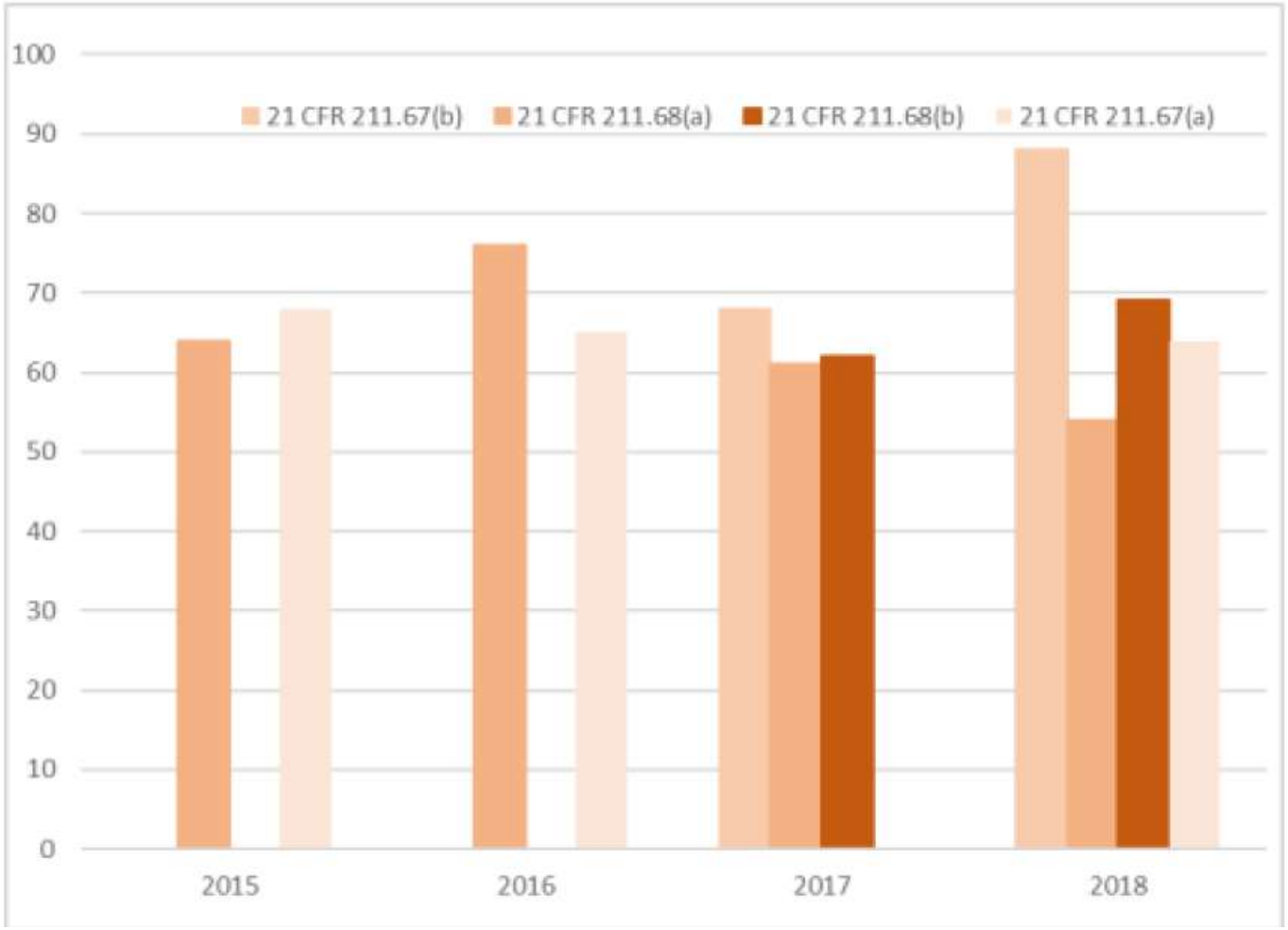
- Processes and procedures
- Adherence and gap evaluation
- Laboratory controls
- Investigation of failures
- Impact assessment & remediation



FDA-483: Top 10 Citations

(Equipment) garnering more attention

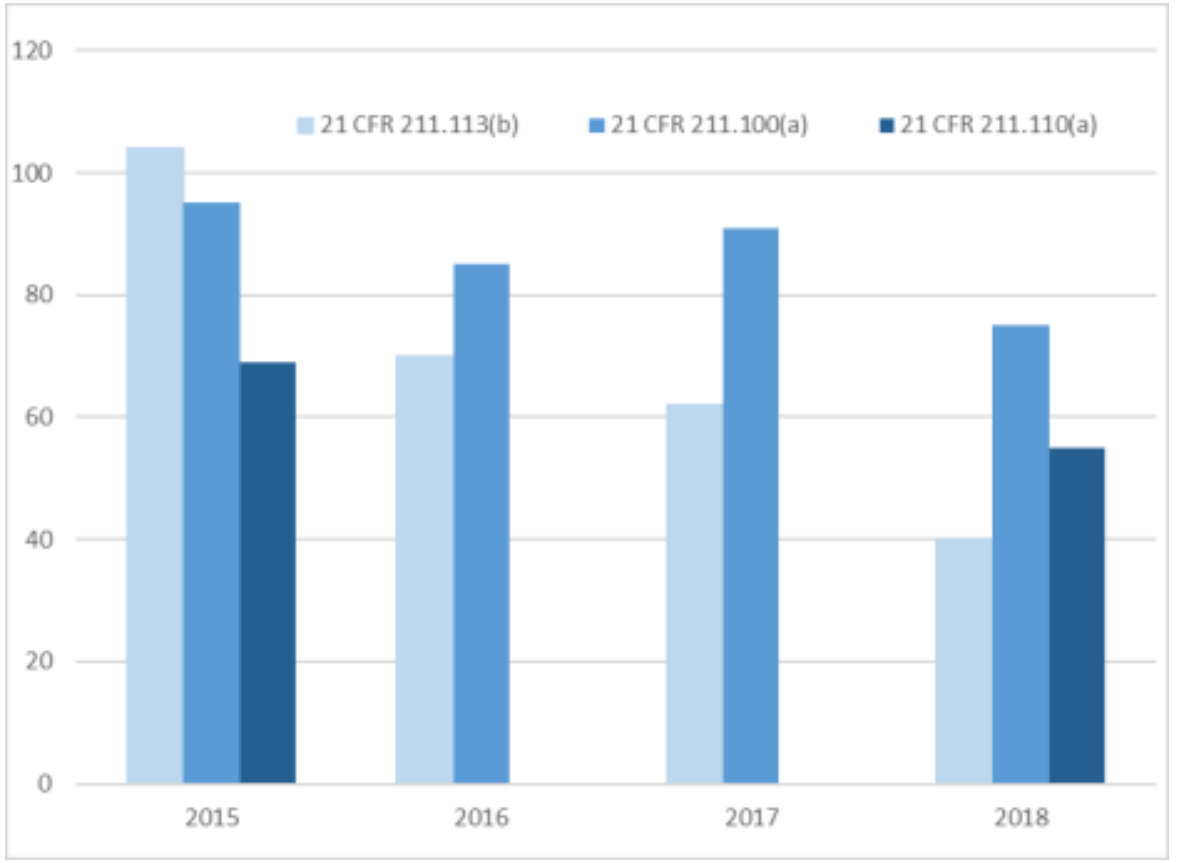
- Procedure & operations for sanitization, cleaning, maintenance of equipment utensils
- Calibrating automated, mechanical, electronic to ensure performance
- Controls on computerized systems to limit access



FDA-483: Top 10 Citations

(Production & Process Controls) still a factor

- Downward trend in ‘Procedures for sterile drug product’
- Gaps noted with control procedures intended to compensate for variability (monitoring, validation insufficient)
- Absence of written procedures continues to be a concern



*Not in top 10 citations for FY2018

Integrated Manufacturing Assessments
Case Study 1

Targeted inspection and in time deficiency correction for a modified release tablet

- Review observation: Lack of control for the hole depth during laser drilling
- Inspection observation: Laser power level identified as critical for the hole depth but not monitored and recorded
- Mitigation: Laser power is controlled and P.3 section of the NDA was revised

Case Study 2

Inspection to cover new product type leads to impact on IQA team's assessment

- Review observation: Facility has poor inspectional history and no approved products for proposed dosage form
- Inspection observation 1: Concerns over testing failures identified during inspection of manufacturer led to coverage of adjacent testing facility
- Inspection observation 2: Coverage of testing facility identified in appropriate averaging of results hiding OOS's, concerns over dissolution method robustness, missing dissolution timepoints
- Outcome: Application was issues a Complete Response as drug product performance could not be established without appropriate dissolution information
- Applicant needs to improve method and demonstrate data reliability in the resubmission

What can you do at your facility?

- Operate within state of control following regulations and policies
- Review events, understand trends, investigate when needed
- Ensure documented scientific evidence supports conclusions for investigations
- Manage product lifecycle by looking at key post market information
- Have a robust PQS
- Have adequate methods to control raw data/prevent data integrity issues

New Inspection Protocol Project (NIPP)

Emerging standardized paradigm, will gather data (risk and rule based) to inform "quality intelligence" of sites and products.

General Principles

- Gather readily accessible, interpretable, and analyzable data
- Develop a tool to gauge state of quality maturity
- Develop a data-rich inspection report
- Role of the investigator is unchanged

Scope

- Manufacturing facility inspections:
  - Pre-approval & surveillance
- Types of drugs:
  - sterile & terminally sterilized
  - Non-sterile
  - Active ingredients

https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-strengthen-and-modernize-agencys-oversight

Summary: Product Specific Inspections

Pre-approval Inspections

- Conducted per Compliance Program - CP 7346.832 to establish
  - Readiness for manufacturing
  - Adherence to application commitments
  - Authenticity and accuracy of data submitted in applications

Post approval Inspections

- Conducted per Center assignment Completed validation activities (e.g., PD, PPQ)
- Execution against application commitments
- Confirm changes, if any, are being managed under quality oversight and being appropriately reported
- Confirm no significant quality issues impacting product have arisen

Challenge Questions:

- **What are the 3 objectives of a Pre-approval inspection?**
  - -Objective 1: Readiness for Commercial Manufacturing
  - -Objective 2: Conformance to Application
  - -Objective 3: Data Integrity Audit

- **What are the primary focus areas for a Post-approval inspection?**
  - -Product specific inspection
  - -Process validation for the product
  - -Changes to manufacturing or specs after approval and how the firm is managing the change

Thank You

- Vidya Pai
- Derek Smith
- Lawrence Yu
- Rapti Madurawe
- Rosa Motta
- OPMA and OPQ Assessment Teams