Deficiencies and Observations from Facility Evaluations And Inspections

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Overview

- Types of inspections
- Discuss coverage and recommendation
- Trends in outcomes
- Facility assessment for ANDAs
- Wrap-up

FDA Inspections 101

FDA Inspections

- An official examination of a facility to determine compliance with FDA laws and regulations*
- Confirm FACTS
- Collect EVIDENCE
- Evaluate CONFORMANCE

Inspectional Basis

- Surveillance (Routine)
- For Cause (Directed)
- Preapproval
- Post approval

Authority to perform inspections per Federal Food, Drug, and Cosmetic Act, Sec. 704 "Factory Inspection".

Product Specific Inspections

Pre-approval Inspections

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

- Firm may have completed Stage 2a or 2b of process validation (i.e., qualification).

Post approval Inspections

- Conducted per Center assignment

Completed validation activities (e.g., PD, PPQ)

- Execution against application commitments
- Confirm equipment, operations and controls are as described in CMC submission; changes, if any, are being managed under quality oversight and being appropriately reported
- Confirm no significant quality issues impacting product have arisen

Inspection workflow

- Initiate
  - Issue Notice of Inspection (Form FDA 482; domestic only) • Display Credentials • Explain purpose & agenda
- Conduct
  - Tour facility • Seek details • View operations • Review operations and records •Collect evidence and samples (as needed) • Daily wrap-up
- Close out
  - Summarize inspection findings • Issue FDA 483, Inspectional Observations (if needed) • Document promised corrections • Ensure firm understands obligations.

FDA 483

Inspectional Observation List

- An FDA 483 is used to list specific significant observations
- Based on investigator's judgment
- Indicates adulteration or potential for same, as a result of
  - poisonous, insanitary ingredients
  - practices with potential to introduce contamination
  - facilities, practices, methods, controls not in conformance with CGMPs to assure safety and quality

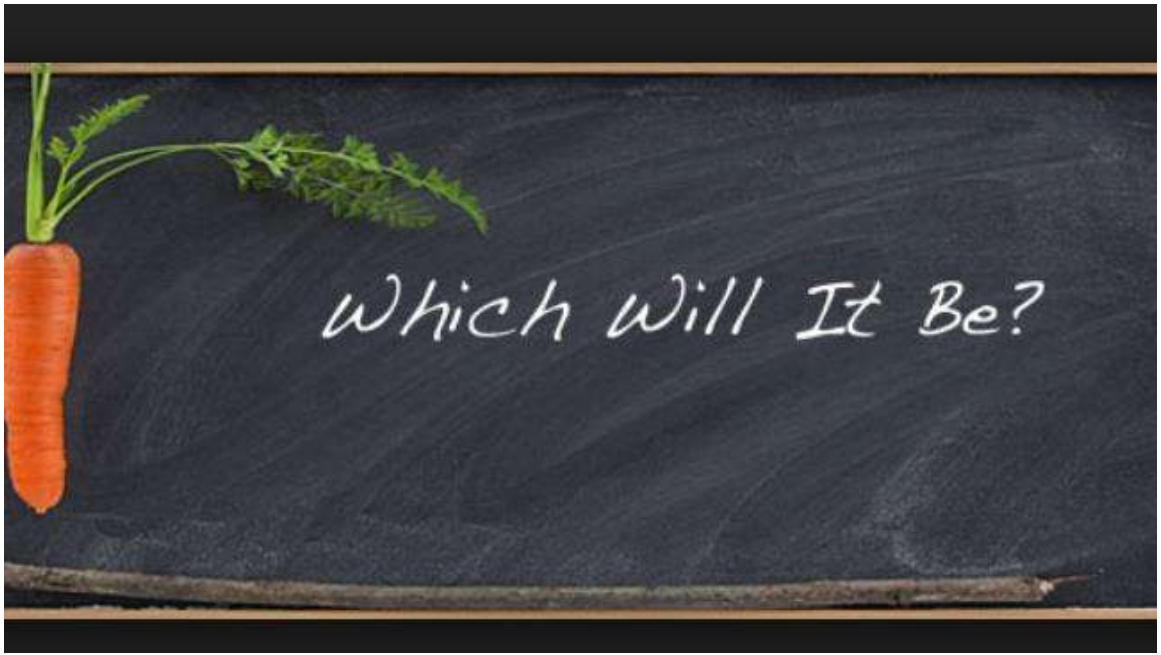
- **Note:** Verbal discussion items may be communicated during and at close of inspection.

Inspection Classification

- NAI – No Action Indicated
- VAI – Voluntary Action Indicated
- OAI – Official Action Indicated

- Pre-approval recommendation – initial field recommendation
- Post-approval recommendation – not usually shared
- Database link: final classification

https://www.fda.gov/iceci/inspections/ucm222557.htm

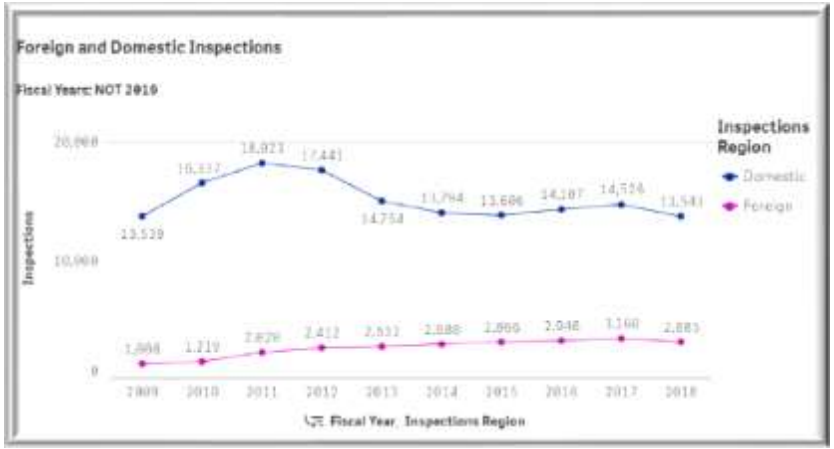


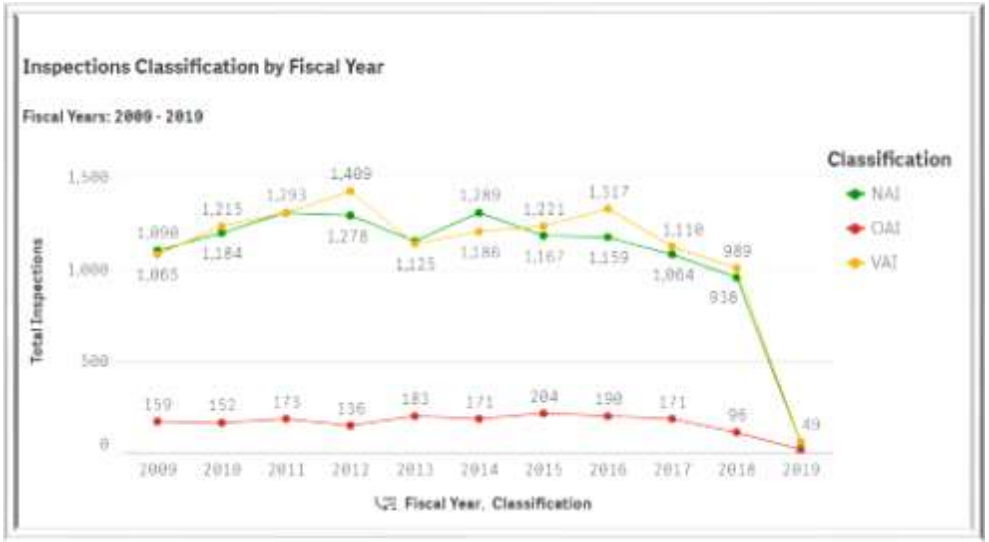
New Inspection Protocol Project (NIPP)

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

Historical Trends - Inspection outcomes

Data only includes surveillance and BIMO inspection outcomes, including for cause and postapproval but not preapproval inspections

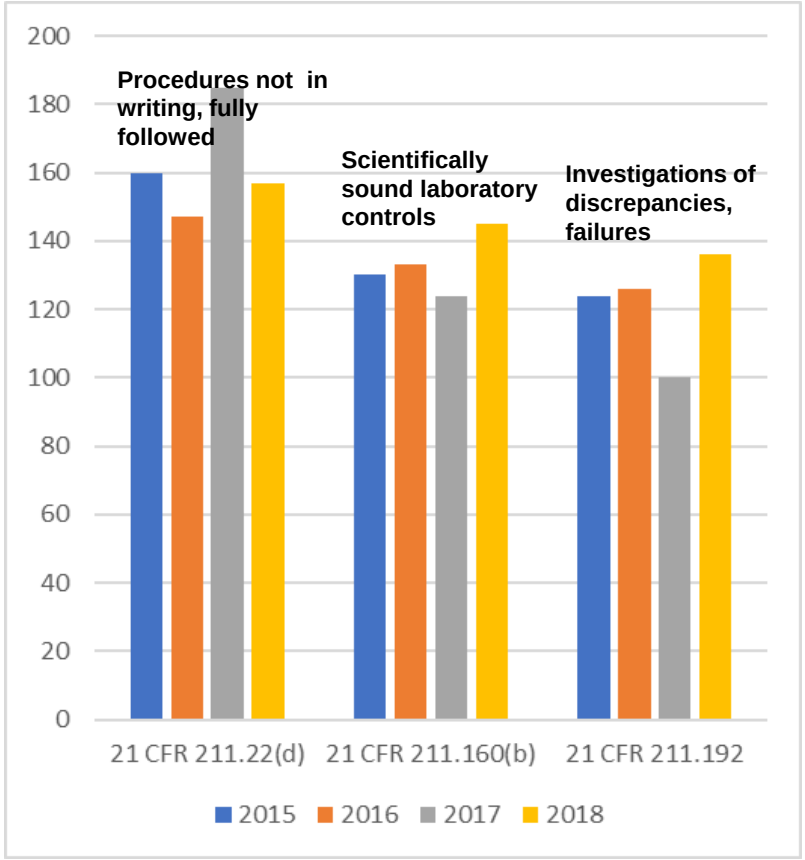




Citations trends - 2015 to 2018

Top 3 citations remain unchanged

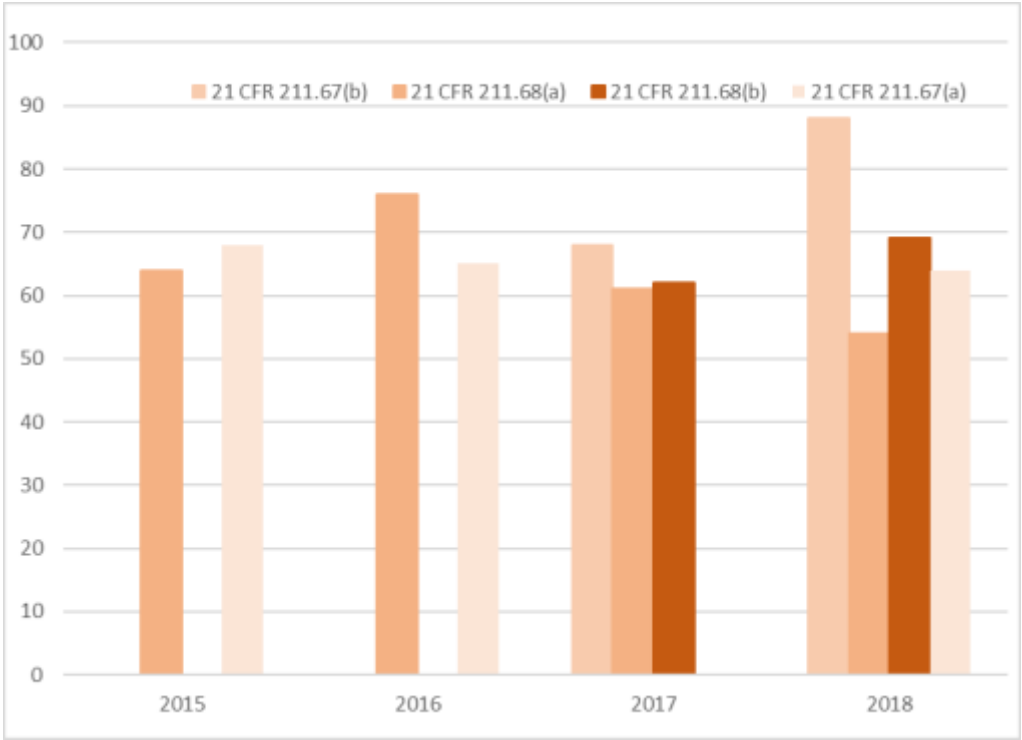
- Quality Unit oversight
  - Processes & procedure inadequate
  - Adherence gaps
- Laboratory controls
  - Scientific and appropriate
  - Assure defects identified
- Investigations into failures
  - Comprehensive
  - Impact & remediation captured



Top 10 citations - trends

Subpart D (Equipment) garnering more attention.

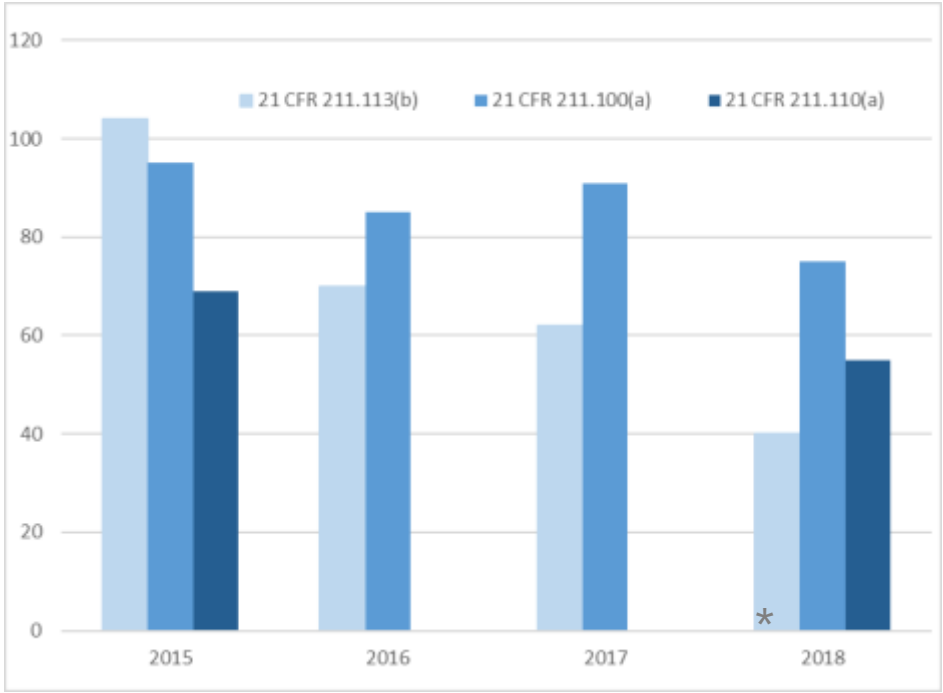
- Procedure & operations for sanitization, cleaning, maintenance of equipment utensils
- Calibrating automated, mechanical, electronic to ensure performance
- Controls on computerized systems to limit access



Top 10 citations - trends

Subpart F (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



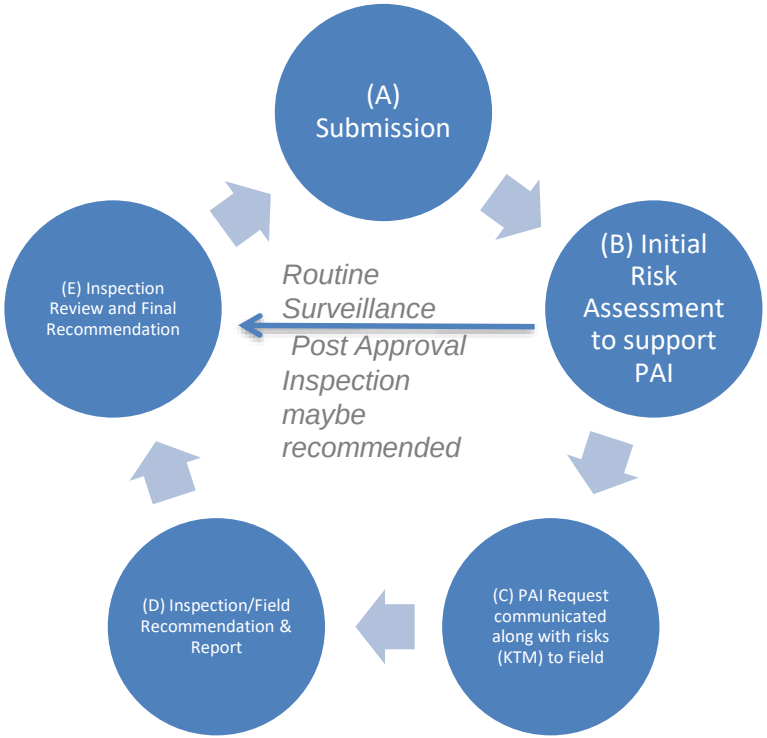
*Not in top 10 citations for FY2018

What does this mean for 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

ANDA Facility Assessment

Pre-Requisite:
Sites must be CGMP compliant to support an approval recommendation.



RACI Chart for Pre-Approval Inspection

Tasks	DFQ/ DPF	DPQ (IQA)	ORA/ Pharm	CDER	ORA
Conduct facility evaluation	R	C	I	A	
Assess accuracy and integrity of the application	C	R	I	A	
Select facility for inspection	R	C	C	A	
Develop inspection strategy	C	R	C	A	
Schedule inspection	I	I	R		A
Conduct inspection	C	C	R		A
Issue FDA 483 as necessary	C	C	R		A
Complete inspection report	C	C	R		A
Review the inspection report and make recommendations	C	R	C	A	
Monitor facility status	R	I	I	A	
Issue NAI/VAI as appropriate	C	R	C	A	
Provide facility recommendation	R	I	I	A	

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/UCM574362.pdf

Facility Review Communications

Submission Receipt — Timely Consult and Information Request (TCIR)

- Incomplete information (FEI, DUNS, address, status)
- Contradictory information in 356h and Module 3
- Supply chain role ambiguous; or gap noted

Mid Review — Discipline Review Letter (DRL)

- Facility issues related to preapproval inspections communicated
- Inspected facility may receive a “RAI – Request for Additional Information”
- Amendments introducing new sites, roles reviewed – goal dates maybe updated

ANDA Action — Action Letter

- Final communication of facilities recommendation for review cycle
- Follow-up OPF Post Action memo indicating outstanding issues sent to inspected facility

Facility Deficiency

INADEQUATE MAJOR: '***require substantial expenditure of FDA resources to re-evaluate the facilities and potentially trigger additional inspections***'

- Complete Response will name Facility/Reason
  - Preapproval withhold
  - CGMP withhold
  - Recommendation from a consult (including device)
  - Facility not performing function
  - Facility not Ready
  - Submission missing critical facility

Successful Preapproval strategies

Withhold reasons: Reference CPGM 7346.832 (Part V)

- Equipment/controls present & operational
- Manufacturing/control instructions supported and details incorporated batch records
- Complete, successful method validation or verification
- Validation is representative, changes if needed instituted
- No missing, misrepresented, non-representative information for submission batches (stability, processing conditions, BE batch information)

Wrap up

- Adopt a holistic systematic process for the assessment, control, communication and review of risks to product quality across the product lifecycle.

- Proactive management of facility risks will ensure patient access to quality medicines and sustained market success.

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- Questions, comments:
  - CDER-OPQ-Inquiries@fda.hhs.gov

Thank you for your attention!


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