

Ensuring Quality over the Product Lifecycle: Risk-based Product Specific Inspections in OPQ

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Objectives

- Provide overview and compare drug inspection programs
- Review inspectional expectations for different application types
- Discuss how product-specific inspections fit into OPQ's Integrated Quality Assessment (IQA) and the Product Lifecycle

Polling Question

D2S3-1

View Votes

Edit

End Poll

D2S3-1: What was the reason for your last FDA inspection?

<input type="radio"/> Pre-approval inspection; your firm was named in the CMC section of A/NDA or BLA	<div></div>	0%	(0)
<input type="radio"/> Post-approval inspection	<div></div>	0%	(0)
<input type="radio"/> Surveillance inspection	<div></div>	0%	(0)
<input type="radio"/> For-cause; i.e. your firm had a recall or submitted an increased number FARs to the FDA recently	<div></div>	0%	(0)
<input type="radio"/> Not sure	<div></div>	0%	(0)
<input type="radio"/> Have not been inspected by the FDA, yet!	<div></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

☐ Broadcast Results

Major CGMP Inspection Types

- Product-specific
 - Pre-approval
 - Post-approval
- Surveillance
- For-cause or directed

Product-specific Inspections and Integrated Quality Assessment (IQA)

- IQA team will provide aligned, patient-focused and risk-based drug product quality recommendations for BLAs, NDAs, and ANDAs, inclusive of drug substance, drug product, microbiology, manufacturing, and facilities.
- Product-specific inspections are a part of the overall quality assessment prior to approval
 - Knowledge sharing between IQA team and inspection team to contribute to OPF final recommendation on facility status for a submission
- After approval, product-specific inspections allow the on-site lifecycle assessment of the risk mitigation strategy employed by the firm, and will also permit verification that any uncertainties or concerns identified by the IQA team have been addressed as commercial scale manufacturing commences

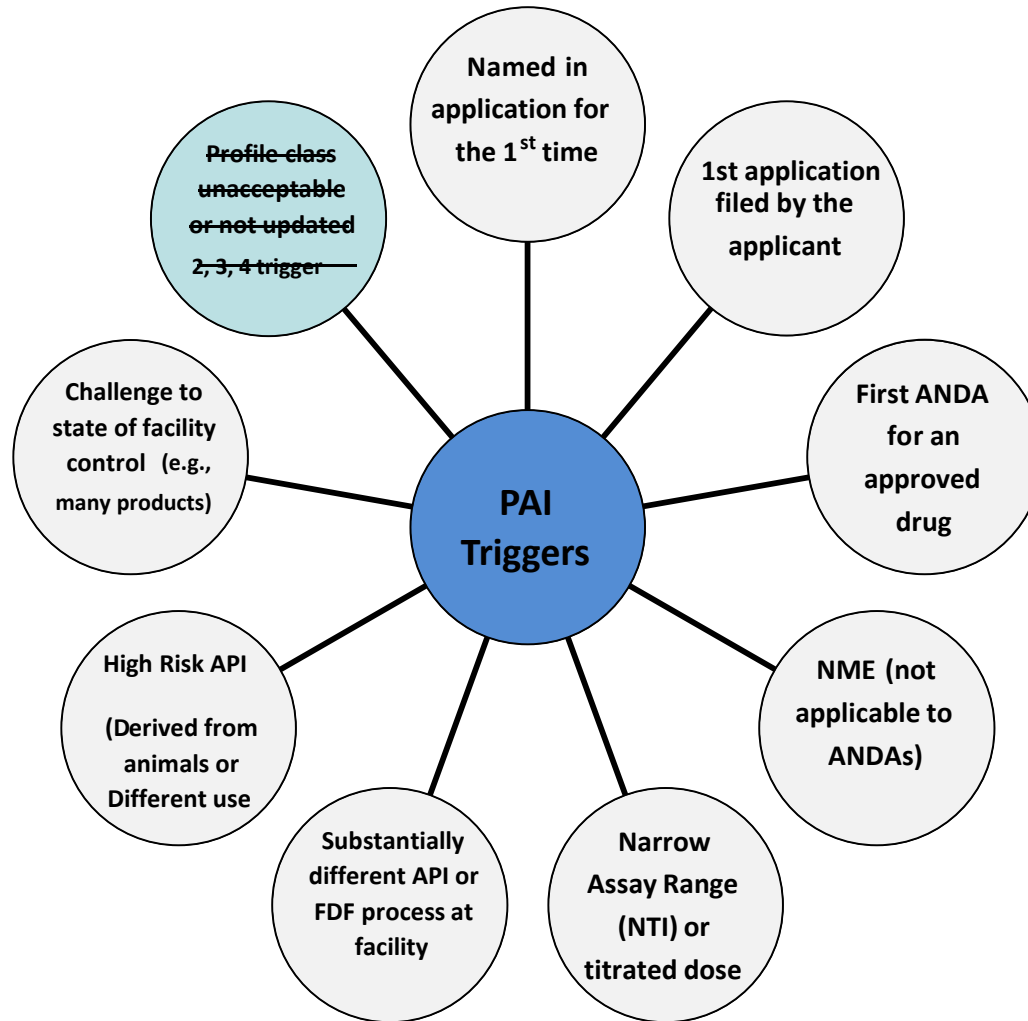
Pre-approval Inspections (PAI) Compliance Program (7346.832)

- **§§ 505(d) and 505(j)(4)(A) (21 U.S.C. §§ 355(d)(3) and 355(j)(4)(A))**
 - The Food, Drug, and Cosmetic Act provides that FDA shall issue an order refusing to approve the application...if the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found inadequate to ensure and preserve its identity, strength, quality, and purity.
- Contributes to FDA's assurance that the manufacturing establishment(s) supporting an application are capable of manufacturing a drug and that submitted data are accurate & complete
- Publicly available CPGM defines program expectations
 - Defines criteria for on-site inspection versus desk file review
 - Discusses coverage during inspection and provides guidance for inspection outcomes

Benefits of PAI Program

- Verification of veracity of data submitted in the application
- Determination of significant issues in manufacturing not reported in the application
- Actual verification of condition of manufacturing facilities, equipment, and processes as described in the application
- Assurance that controls are in place prior to approval and distribution
- Firm's anticipation of inspection to determine: readiness to manufacture; veracity of data; adherence to application commitments, drives firms to be ready for PAI and to pass inspection
- Resolution of issues prior to approval – leverage
- Prevent poor quality products from reaching market

PAI Determination



Priority PAI Criteria per current CPGM 7346.832

PAI Determination

- Not all priority criteria automatically trigger a PAI
- IQA team assessment of risk factors outside of priority criteria in CPGM factors in to final decision
 - Product Risk Factors Considered
 - Known issues with the RLD
 - Intended patient population
 - Breakthrough therapy or drug shortage
 - Manufacturing Process Risk Factors
 - Complex manufacturing process
 - Lack of development data or detailed manufacturing instructions
 - Facility Risk Factors
 - Inspectional history for relevant operations in application
 - Product quality defect signals (e.g. FARs, Recalls)

PAI Objectives

Objective 1: Readiness for Commercial Manufacturing

Determine whether the establishment(s) has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.

Objective 2: Conformance to Application

Verify that the formulation, manufacturing or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the CMC section of the application for the biobatch (and other pivotal clinical batches, when applicable), the proposed commercial scale batch, and the API(s).

Objective 3: Data Integrity Audit

Audit the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, biobatch data) were submitted in the CMC section such that CDER product reviewers can rely on the submitted data as complete and accurate



PAI Outcomes

- Lead investigator will make an initial recommendation at the conclusion of the inspection:
 - Recommend Approval
 - Indicates that the inspection found no significant issues
 - Response to observations is important
 - Recommend Withholding Approval
 - Investigators observed that the site is not CGMP compliant, information in CMC is not consistent with site records, or information submitted is not accurate and complete.
 - Response to observations is critical
- REMINDER: OPQ/OPF makes the final recommendation on status of the facilities. Facility assessment is part of the overall OPQ quality recommendation and should not be considered as having a separate status

Impact of Pre-Approval Inspections

(based on actual inspections)

- Identify lack of conformance to application and data integrity issues, for example:
 - Falsified data (complete fabrication of sterility testing, environmental monitoring, WFI testing, biological indicators for sterilization, bioburden samples, endotoxin testing, media fills)
 - QA approval of incomplete and/or erroneous laboratory data
 - Changes of specification (widening) not reported to application
 - Testing into compliance

Impact of Pre-Approval Inspections

(based on actual inspections)

- Identify firms not capable of manufacturing products, for example:
 - Equipment not installed
 - Lack of clearly defined responsibilities between sponsor and contract manufacturer listed in application
 - Lack of appropriate controls to ensure quality
 - Multiple batch failures not reported in application

12 Reasons to Recommend Withhold

(per PAI CPGM 7346.832)

- Significant Data Integrity deficiencies
- Serious CGMP concerns with bio- or submission batches
- Significant differences in manufacturing process for pivotal clinical batches and submission batches
- Lack of complete manufacturing instructions or data to support instructions
- Lack of capacity to manufacture for application
- Failure to meet application commitments

12 Reasons to Recommend Withhold

(per PAI CPGM 7346.832)

- Commercial scale process validation issues indicating process is not under control and appropriate changes not made
- Facility has not demonstrated product can be reliably manufactured at commercial scale to meet quality attributes (when data available)
- Method validation/verification problems
- Incomplete records for submission batches
- Stability failures
- Failure to report adverse findings or failing data without appropriate justification

PAIs for NDAs and ANDAs

- Often limited or no commercial manufacturing
- More focus 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)
- Trend toward more CDER staff involved in the inspection

PAIs for BLAs

- Inspections performed by BLA review team from OPF and OBP who have a focus on Product, Microbiology and CGMP aspects of manufacturing that product. Investigator is part of the review team.
 - Based on resources, ORA may participate and/or lead as well
- Process validation complete at time of submission
- Commercial manufacturing during PAI

PAIs for Combination Products

- CGMPs for combination products
 - 21 CFR Part 4
 - a firm shall comply with all applicable CGMP requirements per constituent part (drug, device, biologic) included in the combination product
 - or base CGMP system plus additional “called out” sections
 - Intent to streamline demonstrating compliance and to help ensure appropriate implementation of requirements while avoiding unnecessary redundancy

PAIs for Combination Products - Called Out Sections

- If operating under Drug CGMP,
 - 820.20 (management)
 - 820.30 (design)
 - 820.50 (purchasing)
 - 820.100 (CAPA)
 - 820.170 (installation)
 - 820.200 (servicing)
- If operating under Quality Systems Regulation (Device),
 - 211.84 (incoming testing)
 - 211.103 (calc of yield)
 - 211.132 (OTC package)
 - 211.137 (exp dating)
 - 211.165 (release testing)
 - 211.166 (stability testing)
 - 211.167 (special testing)
 - 211.170 (reserve samples)

PAI Expectations for Combination Products

- Manufacturing of constituent parts will be inspected to its respective CPGM
- Manufacturing of finished combination products may be inspected to multiple CPGMs
- Consider potential differences in individual Center expectations (e.g. process validation)

Pop Quiz:

D2S3-2

View Votes

Edit

End Poll

D2S3-2: The FDA expects the following to be complete at the time of PAI:

<input type="checkbox"/> Stage 1 Process Design	<div></div>	0%	(0)
<input type="checkbox"/> Stage 2A Design of Building and Facilities	<div></div>	0%	(0)
<input type="checkbox"/> Stage 2B Process Performance Qualification	<div></div>	0%	(0)
<input type="checkbox"/> Stage 2B PPQ, for BLAs only	<div></div>	0%	(0)
<input type="checkbox"/> Stage 3 Continuous Process Verification	<div></div>	0%	(0)

☐ Broadcast Results

Post Approval Audit Inspections (PoAI) Compliance Program (7346.843)

- Provide continuing inspection coverage of products marketed under a recently approved application
- Monitor for changes in the production and control practices that occur after approval (6-24 months)
- Coverage is based on reason for inspection (e.g. pre-approval inspection, PPQ concerns, past history)
- Trend towards an increase in post-approval inspections as a part of OPQ's lifecycle approach to quality assessment

Purpose of PoAI

- Provides assurance that:
 - A drug product is manufactured according to the approved application
 - The manufacturing process is maintained in a state of control
 - Subsequent changes have not adversely affected drug quality
 - Data submitted in support of changes are accurate and authentic.
 - Confirm that changes are implemented appropriately (i.e. change control & CGMPs)
 - Confirm that changes are reported appropriately to the Agency (i.e. supplements are filed)
 - Verify application commitments are fulfilled.

Why Post-Approval?

- At the time of the PAI, the firm has **limited** knowledge about the product & process.
 - May have purchased 1 – 3 lots of API.
 - Product development batches (1 – 2).
 - Submission/stability batches (1 – 3).
- The vast majority of firms have not completed PPQ at the time of the PAI.

Why Post-Approval?

- Within 2 years of approval:
 - Completed PPQ
 - Manufacture of commercial scale conformance lots
 - Initiated commercial distribution
 - Ongoing continuous process verification
 - Continually evaluates process to determine the need for improvements
 - Implement systems to ID new sources of variability and prevent failure
 - Manufactured additional commercial batches
 - More process understanding.
- Increased information regarding the commercial scale manufacturing enhances inspectional assessment

Example: Raw Material Variability

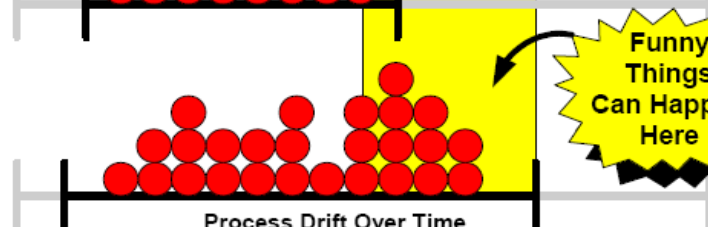
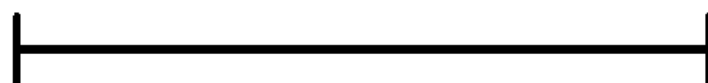
Raw Materials: Typical Historical Experience with Physicochemical Properties

USP
Limits

R&D
Development
Experience

Initial Launch
Experience

Long-Term
Commercial
Experience



}

Pre-Approval

}

Post-Approval

Post-Approval Inspection Determination

- PAI was not performed.
- PAI revealed significant deficiencies but didn't meet the threshold of a withhold.
- Firm promised corrective actions to significant PAI deficiencies
- Stage 2 PPQ of process validation not completed at the time of the PAI.
- Firm has a history of frequent PAI deficiencies (i.e. scale up, development).
- Complex manufacturing process.
- First application filed by the sponsor.
- New profile class for the establishment.
- High rate of drug quality reports (FARs / MEDWATCH)
- IQA team recommendation due to complexity or residual risks/uncertainties

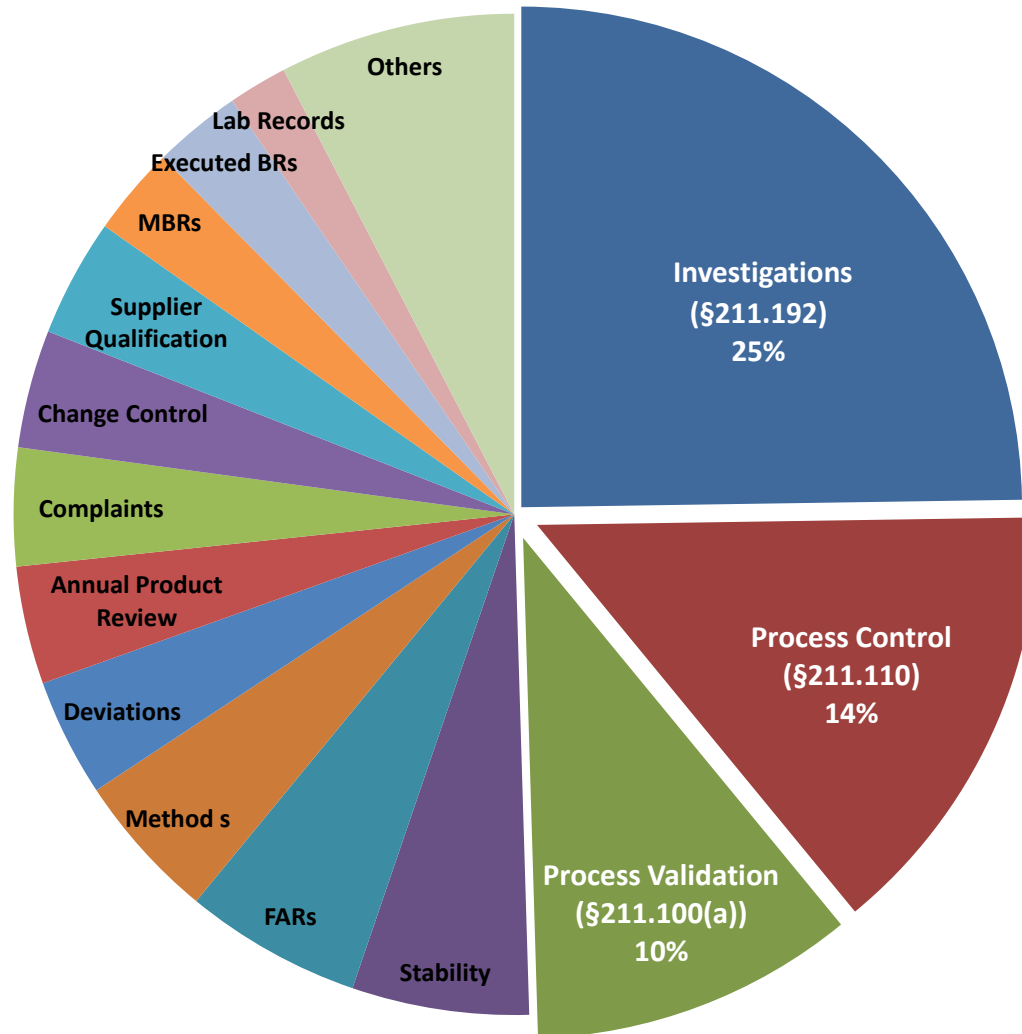
Post-approval Inspectional Coverage

- PV Stages 2 & 3: Process Performance Qualification (PPQ) and Continued Process Verification (CPV);
- Changes in the production and control practices;
- Supplier qualification;
- Laboratory (in-process/release/stability testing, methods, OOS results);
- Quality management/correction of quality defects; and
- Quality management/prevention of quality defects.

PoAI Outcomes

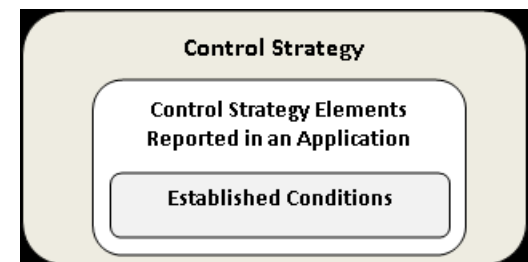
- Positive and negative findings will feed into the pre-approval facility risk assessments
- Expected application updates via supplements as appropriate
- Potential regulatory action depending on significance of negative findings

What are the top PoAI FDA-483



General Findings

- Processes failing during scale up and PPQ
- Identify new relationships between material attributes and process parameters, and quality attributes
- Dubious quality system decisions in response to failure or new knowledge
- Reduction in monitoring
 - Blinds companies from identifying process improvements
 - Conflicting understanding of control strategy vs. approved process



Drug Manufacturing (Surveillance) Inspections Compliance Program (7356.002)



- In addition to product-specific post-approval inspections, facilities are evaluated via surveillance inspections
- Provides for evaluation of CGMP compliance of the facility
- Inspections are systems-based and control of all systems helps to ensure production of drugs that meet intended safety, identity, strength, quality and purity characteristics

What are the Systems?

Six systems:

- Quality
- Facilities and Equipment
- Materials
- Production
- Packaging and Labeling
- Laboratory Controls

21 CFR 211:

- Subpart B - Organization and Personnel
- Subpart C - Buildings and Facilities
- Subpart D - Equipment
- Subpart E - Components and Container/Closures
- Subpart F – Production and Process Controls
- Subpart G - Packaging and Labeling
- Subpart I - Laboratory

Surveillance Inspection Coverage

Full inspection (Quality + 3):

- Initial inspection
- History of noncompliance
- Significant changes
 - New technologies, equipment, facilities
- Follow-up to a Warning Letter
- Revert to an Abbreviated Option with District Concurrence

Abbreviated (Quality +1):

- When not using the Full Inspection Option
- Surveillance inspections
- Adequate for routine coverage
- Rotate systems with the Abbreviated Option – District will monitor

Surveillance Inspection Determinations

A Mandate for Risk-Based Scheduling:

“The Secretary, acting through one or more officers or employees duly designated by the Secretary, shall inspect establishments described in paragraph below:

(1) that are engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs (referred to in this subsection as ‘drug establishments’)

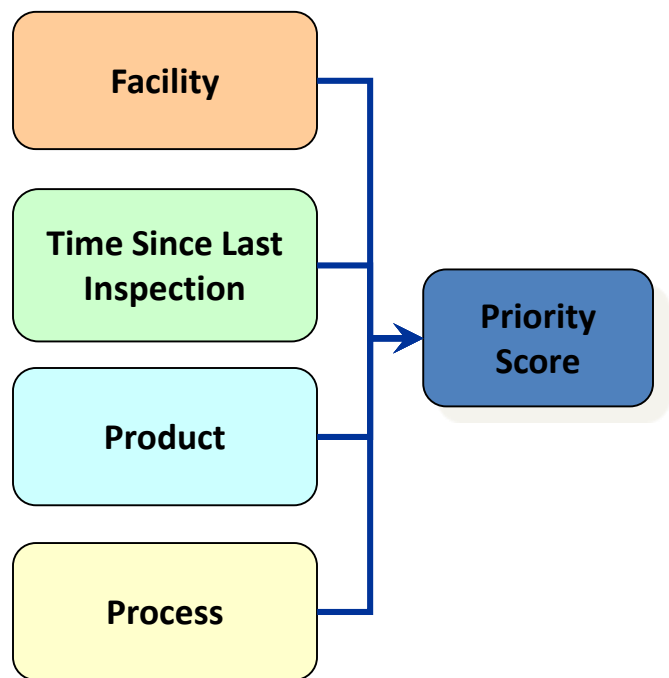
in accordance with a risk-based schedule established by the Secretary.”

Risk Factors Impacting Frequency (FDASIA Sec 705)

- (A) The **compliance history** of the establishment.
- (B) The record, **history**, and nature **of recalls** linked to the establishment.
- (C) The **inherent risk of the drug** manufactured, prepared, propagated, compounded, or processed at the establishment.
- (D) The **inspection frequency and history** of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years.
- (E) Whether the establishment has been **inspected by a foreign government** or an agency of a foreign government recognized under section 809.
- (F) **Any other criteria deemed necessary** and appropriate by the Secretary for purposes of allocating inspection resources.”

Site Selection (Surveillance) Model

- Data Sources
 - Inspection-related data
 - Firm information (size, location, history)
 - Firm activities and process
 - Processes previously covered
 - Inspection outcome
 - Import data for international sites
 - Volume and import lines
 - Common products
 - Registration and Listing data
 - Application-based data
 - Approved firms and processes for FDA NDA, ANDA and BLAs
 - Compliance data
 - Enforcement actions, recalls, etc.
 - Quality deviation reports



For-Cause/Directed Inspections

Anything other than a routine inspection (PAI, PoAI, surveillance)

- Investigate a specific problem that has come to FDA's attention:
 - NDA Field Alert report
 - Recall
 - Adverse event cluster (e.g., heparin)
 - or other “event”
- Generally the focus is on the specific event and the company response
- Determine state of control in a specific area of processing (e.g., verify correction of previous deficiencies)

Summary

- PAIs are product-specific inspections driven by the OPQ IQA team's assessment of the product, process, and facility risks for the application.
 - Application/Facility is acceptable for approval from surveillance perspective - unless facility is classified as OAI
 - But a recent “positive” surveillance inspection (NAI/VAI) does not mean a PAI will not be needed
- PoAIs are product-specific inspections driven by residual risks or uncertainties at time of approval as identified by the IQA team.
 - Independent of surveillance inspections and may occur any time after approval
- Surveillance inspections are not product-specific but assess the pharmaceutical quality system of the facility to ensure CGMP compliance
 - Frequency is risk-based driven by a site selection model
 - PAIs and PoAIs may be combined with a surveillance inspection

Thank you for your attention!



Please complete the session survey:

surveymonkey.com/r/DRG-D2S3

Additional Questions: CDER-OPQ-Inquiries@fda.hhs.gov