Pre-Approval Inspections (PAIs)

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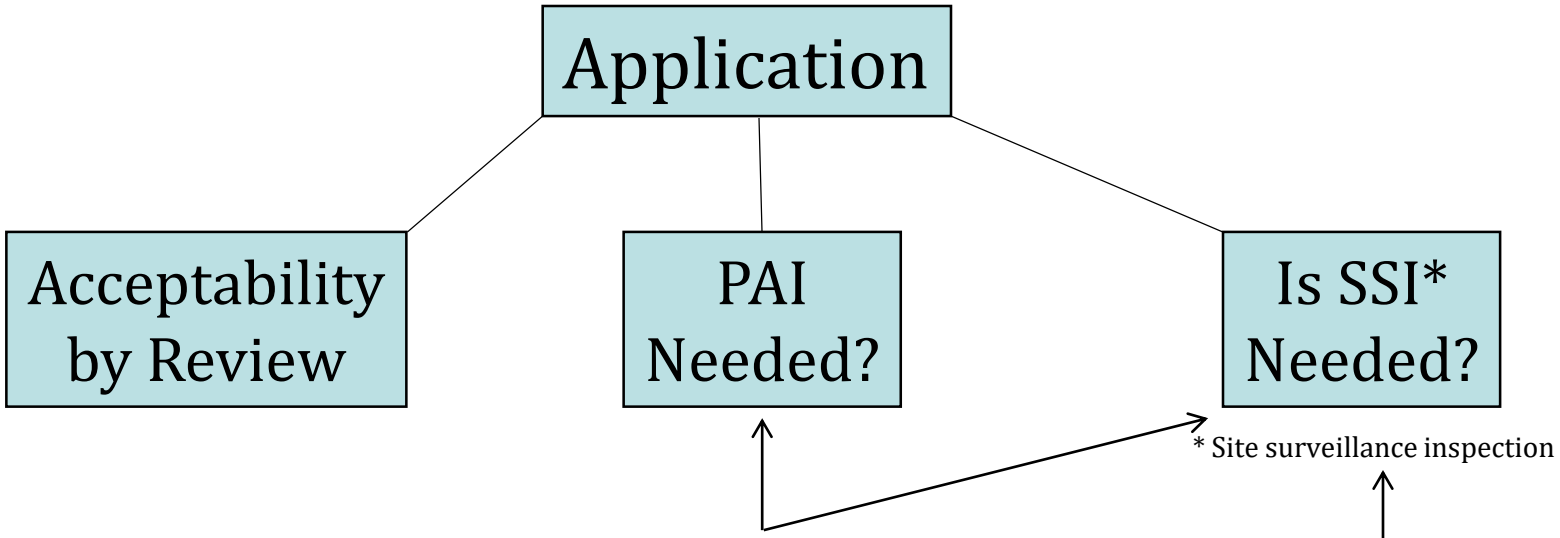
Objectives

- Share current updates on PAI Program
- Compare PAIs to Surveillance Inspections
- Discuss how PAIs fit into OPQ's Integrated Quality Assessment (IQA)
- A little on PAI's and Process Validation

Inspections & Application Decisions



Different focus and decision rules for PAI & SSI

- *PAI decision driven from molecule and technology*
  - *focus on product and data integrity*
- *Surveillance decision previously driven from "2,3,4;" now purely from Site Selection Model (SSM)*
  - *focus on "6 systems"*

Application/Facility is acceptable for approval from surveillance perspective - unless facility is classified as OAI

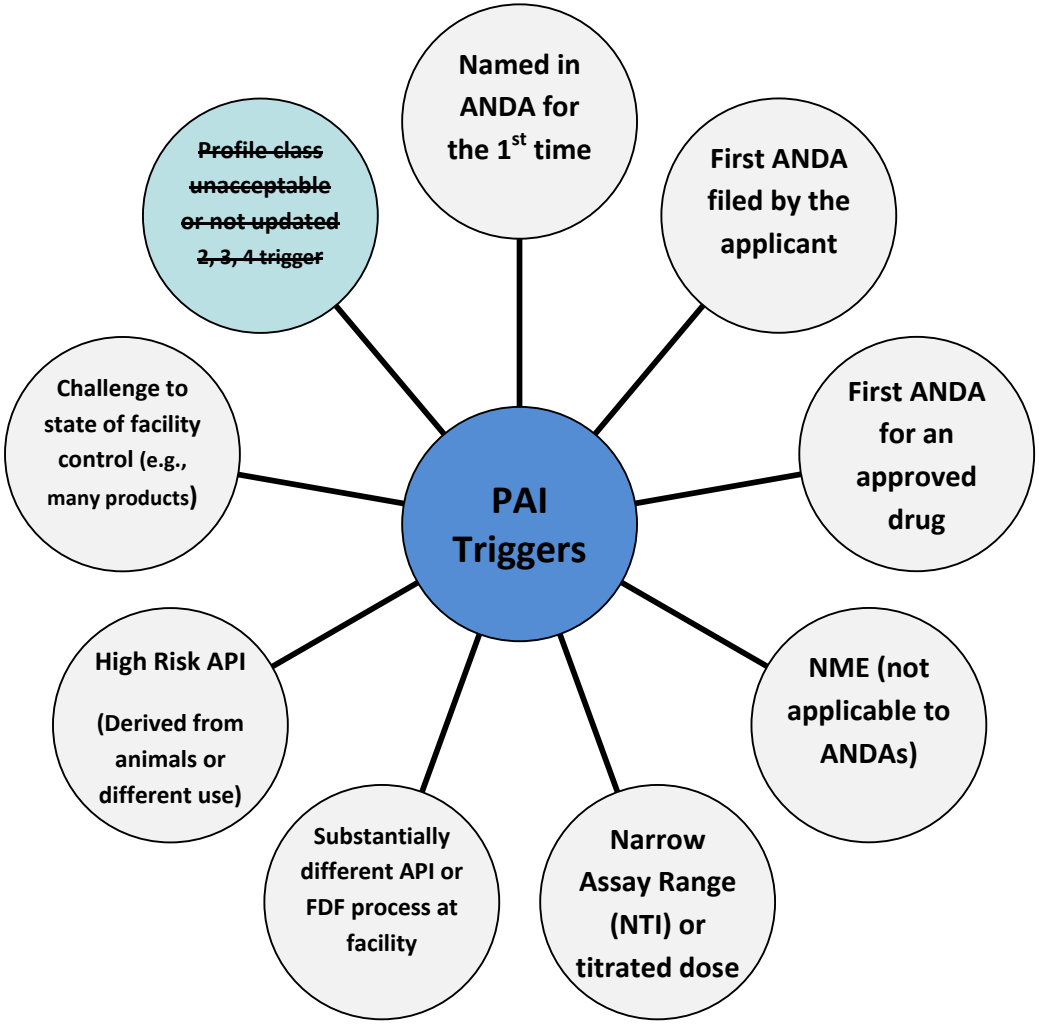
Pre-Approval Inspection (PAI) Program

- Contributes to FDA's assurance that the manufacturing establishment(s) supporting an application are
  - Capable of manufacturing a drug and
  - Submitted data are accurate & complete
- CPGM (Compliance Program) 7346.832
  - on-site PAI and/or file review

Pre-Approval Inspection (PAI) Program

- Program establishes
  - Criteria for deciding if a PAI may be needed
  - On-site coverage
  - Guidance for inspection outcome
- These criteria are distinct and separate from any potential surveillance inspection decision

Priority PAI Criteria*



* As found in current CPGM 7436.832

Why remove "time since last inspection" trigger?

Consider the intent of the PAI program vs. the surveillance program:

- PAI triggers focus on those aspects most relevant to the **specific application** under review
- Surveillance program provides **ongoing** facility assessment, includes pharmaceutical quality system
  - Time since the last surveillance inspection relevant to the surveillance program and is a risk factor in determining when a surveillance inspection should be conducted

A little more on the PAI being product specific

- Limited or no commercial manufacturing in ANDAs
- More focus on development data
- More emphasis on authenticity of data and application commitments
- Process validation
- Application actions are generally administrative
- Trend toward more CDER staff involved in the inspection

FDASIA 705: Risk-based Inspections

FDA "shall inspect establishments…in accordance with a risk-based schedule"

Risk factors:

(A) The compliance history of the establishment.

(B) The record, history, and nature of recalls linked to the establishment.

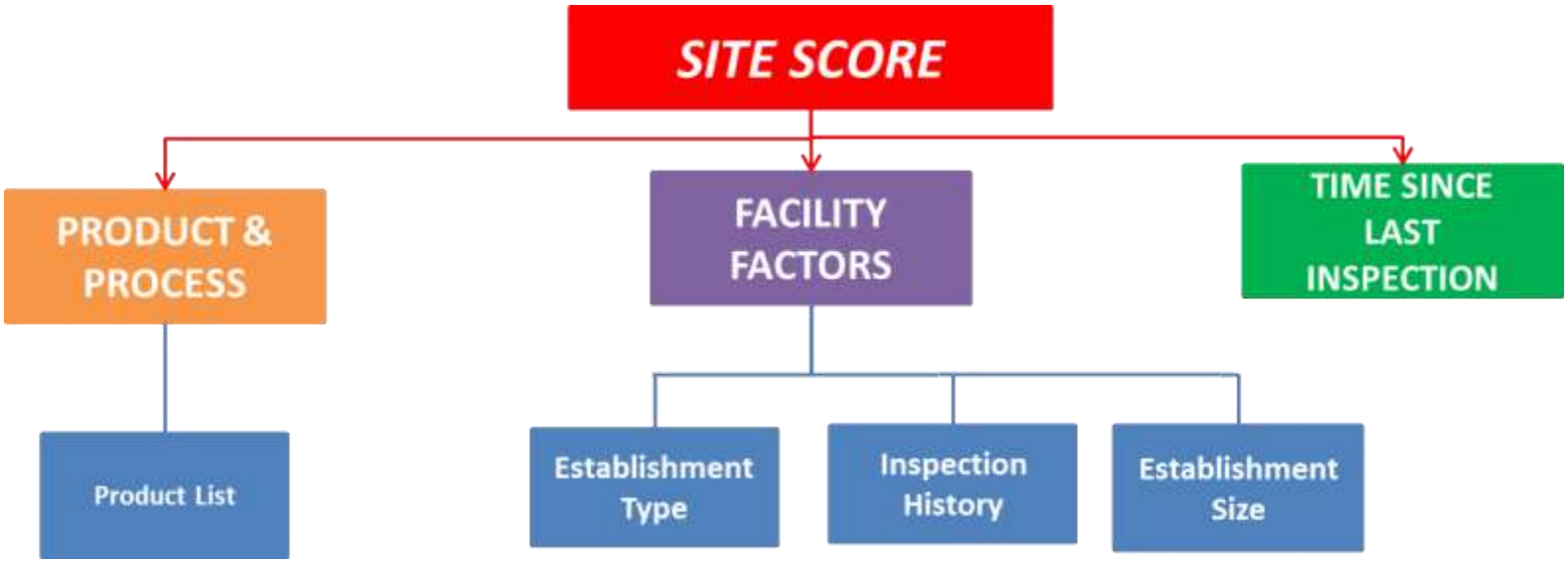
(C) The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment.

(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.

Current Surveillance Model Structure



- Outcome is a score and relative priority ranking of entire inventory
  - Absolute score not relevant (i.e., NOT “high,” “medium,” “low”)
  - Meets risk based parity expectations

PAIs and the Integrated Quality Assessment (IQA)

Integrated Quality Assessment

- IQA team will provide an aligned, patient-focused and risk-based drug product quality recommendations for BLAs, NDAs, and ANDAs, inclusive of drug substance, drug product, manufacturing, and facilities.
- **IQA Teams consist of:**
  - Application Technical Lead (ATL)
  - Regulatory Business Process Manager (RBPM)
  - Discipline Reviewers (includes OPF & ORA)
  - Advisors - Lab (OTR), Policy (OPPQ), Surveillance (OS), etc.

ANDA IQA Team Roles

Role / Task	Responsible*
Scientific Content / Initial Risk Assessment	ATL / IQA Team
Process and Timeline	RBPM
IQA Executive Summary	ATL / IQA Team
Assessment of Drug Substance / DMF	DS/DP Reviewer
Assessment of Drug Product	DP Reviewer
Assessment of the Manufacturing Process	Process Reviewer
Assessment of Facilities	Facility Reviewer
Assessment of Biopharmaceutics	Bio pharm Reviewer
Assessment of Microbiology	Micro Reviewer
Assessment of Environmental Analysis	EA reviewer
Labeling & Package Insert	DP Reviewer
PAI Inspections	ORA Lead / SMEs participate
Lifecycle Knowledge Management	ATL/ IQA Team

* Represents General Cases

PAIs and the IQA team

- A PAI is part of the overall quality assessment performed by the Integrated Quality Assessment (IQA) team
- IQA team members (ORA, OPF, others) share knowledge and participate on PAI
- Inspection findings are fed back into IQA team

PAI and the IQA Team (cont.)

- ANDA Status Point of contact for OPQ is RBPM and for OGD is RPM
- Facility assessment is part of the overall OPQ quality recommendation and should not be considered as having a separate status (as occurred pre-OPQ)
- As part of GDUFA commitments, the PAI is to be complete during the "review" time frames, so that goals are met
  - Make sure the submitted facility information is accurate and complete

One PAI Challenge

Challenge in reporting inspection / PAI outcomes, is when the inspected facility is not the sponsor

- Recommend that quality agreements with CMOs allow for transparent sharing of information, including inspection findings
- FDA also reserves the right to communicate information obtained during inspection of contracted extramural facilities to the application sponsor – per 21 CFR 200.10

So when will my ANDA need a PAI?

- PAI decision is made based on product, process and/or facility specific issues
  - Considering areas of potential risk
  - Based on evaluation of:
    - facility history – inspectional outcomes from most recent inspections; NOT time since last inspection
    - information that was provided in the submission
  - PAIs may also be recommended during review of an application (e.g., critical concern raised by IQA team) or when an amendment is received (e.g., new facility proposed)

Reminder

A recent "positive" surveillance inspection (NAI/VAI) does <u>not</u> mean a PAI will not be needed.

Additional Note: Facility Withdrawal from Pending ANDAs

- Recommend that sponsors consider the impact of requesting to withdraw a facility from a pending ANDA
- The data / information generated at the facility to be withdrawn will factor into OPQ's recommendations to OGD

PAIs and Process Validation

Process Validation: Product Lifecycle Stages

Description of Activities	*Goals*
Stage 1: Process Design	
Lab, pilot, small scale and *scale-up* studies to establish process based on knowledge	Functional understanding between parameters (material and process) and quality attributes
Stage 2: Process Qualification	
▪ Facility, utilities and equipment ▪ Performance Qualification (*evaluate* commercial process design)	Scientific measurable evidence that ▪ product meets specifications consistently ▪ process performance reproducibly meets appropriate limits and standards
Stage 3: Continued Process Verification	
▪ Monitor, collect information, assess during commercialization ▪ Maintenance, continuous verification, process improvement	▪ prompt actions to maintain or improve control ▪ reduce product and process variability

Inspectional Coverage
Process Validation Stage 1

- Process design is the activity of defining the commercial manufacturing process that will be reflected in the master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes. The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

- **This development data is the foundation of the firm's process validation program and is often reviewed during a PAI**

Inspectional Coverage
Process Validation Stage 2

- Process Performance Qualification (PPQ) - achieving a level of confidence that the commercial process and controls consistently result in high quality product and that commercial distribution is justified.
  - **Observation of equipment and reports supporting the qualification of the selected equipment/utilities relevant to the application product**
  - **PPQ protocol**

Inspectional Coverage
Process Validation Stage 3

- Product launch is based on initial knowledge (generally based on development and initial qualification lots)
- More accurately gauge type and scope of variation as each batch is produced
- More accurate measurements of process capability and process understanding
  - **Good change & knowledge management is important**

Inspectional Coverage
Process Validation Stage 3

State of Control ~ Daily Quality Assurance

- "After establishing and confirming the process, **manufacturers must maintain the process in a state of control over the life of the process,** even as materials, equipment, production environment, personnel, and manufacturing procedures change." (FDA PV Guidance)

- **State of control**: a condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

Acknowledgements

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Thank you for your attention!

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

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