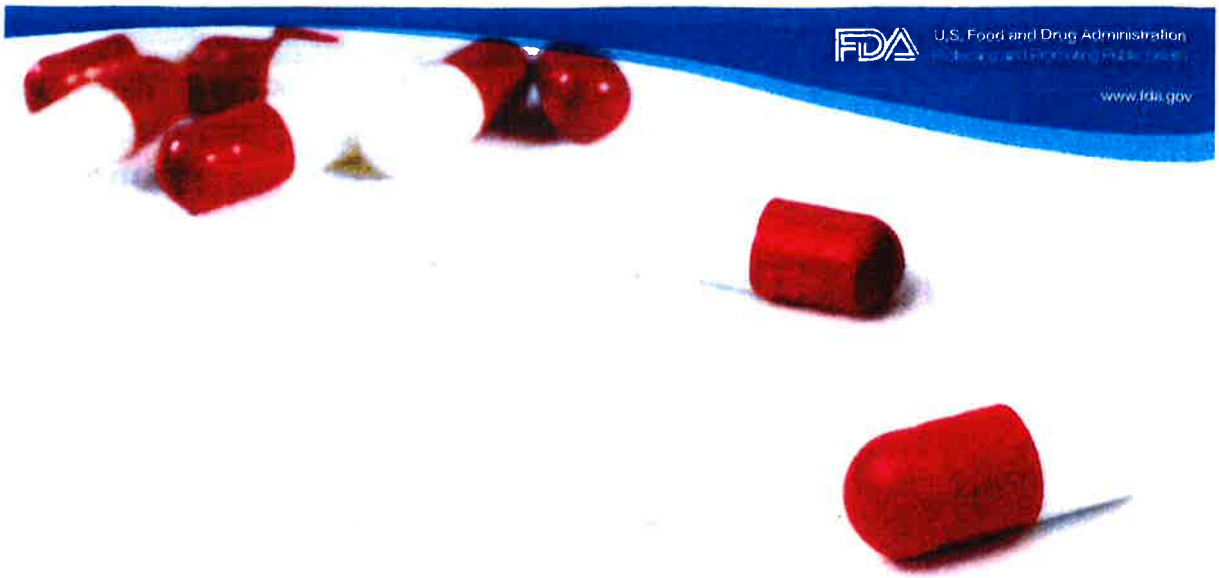

Quality Forum
March 4, 2015

U.S. Food and Drug Administration
www.fda.gov

Welcome Remarks and Introductions

Opening Statement from Dr. Janet Woodcock

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PAI (PRE-APPROVAL INSPECTIONS)

Robert Iser
Director (acting)
CDER/OPQ/Office of Process and Facilities

Pre-Approval Inspection (PAI) Program

- PAI Program contributes to FDA's assurance that the manufacturing establishment(s) listed in an application are capable of manufacturing a drug and submitted data are accurate & complete
- CPGM (Compliance Program) 7434.832 – evaluation of establishments (on-site PAI and/or file review)
- Program establishes criteria for deciding if a PAI may be needed
- This is distinct and separate from any potential surveillance inspection decision

Priority PAI Criteria*

1. Establishment is named in an application to FDA for the **first time**, including establishments that have never been inspected or have been inspected only for non-application drugs;
2. **First application** filed by applicant (for coverage of finished dosage manufacturing and testing);
3. **First ANDA** filed for an approved drug (for coverage of finished dosage manufacturing and testing);
4. Finished product contains a **New Molecular Entity (NME)** (does not apply to supplements);
5. Finished product **content assay has a narrow range** (e.g., 95-105% labeled strength for narrow therapeutic index drugs) or drug is expected to require titrated dosing (does not apply to supplements);
6. Finished product or API is manufactured by a **substantially different manufacturing process or dosage form** than previously covered at the establishment;
7. **API derivation is high risk** (e.g., API is derived from animal tissues) or the intended use has significantly changed (e.g., API previously used in non-sterile product is now intended for a sterile drug product);
8. Numerous application submissions or certain site/process/product changes that are expected to pose **significant challenge to the state of control** of the facility or process; and
9. ~~Profile class status of application product or API is "unacceptable" or not updated via a site inspection within the past **2 years (3 years for control laboratories and 4 years for packaging and labeling)**, for original applications or significant pre-approval CMC supplements.~~

* As found in current CPGM 7434.832

Why remove "time since last inspection" from the PAI triggers?

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

- The surveillance program provides ongoing assessment for all products manufactured at a given facility and includes an assessment of the firm's quality system
- The PAI program is intended to ensure that the facilities named in a specific application are capable of manufacturing and that the data in the application are accurate and complete.
- FDA has revised the PAI triggers to focus on those aspects most relevant to the specific application under review.
- Time since the last surveillance inspection remains most relevant to our surveillance program and will continue to be a risk factor in determining when a surveillance inspection should be conducted.

So when will my ANDA need a PAI?

- Decisions to perform a PAI are 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)
- A recent positive surveillance inspection does not mean a PAI will not be needed.

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
- **One 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

Additional Note:
Facility Withdrawal from Pending ANDAs

- We 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

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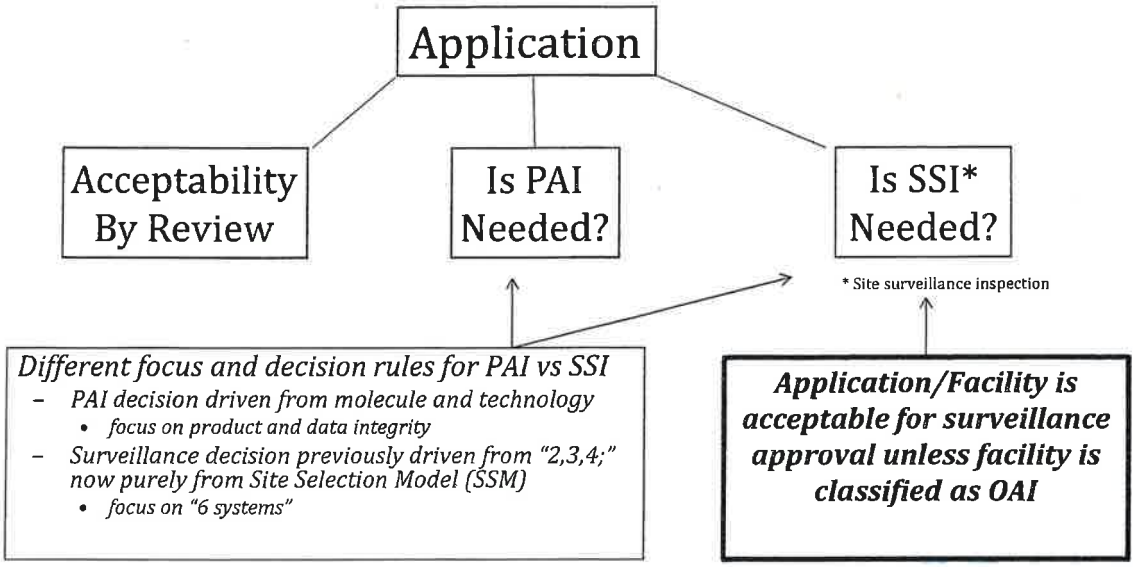
SSI
(SITE SURVEILLANCE INSPECTIONS)

Russell Wesdyk
Director (acting)
CDER/OPQ/Office of Surveillance

For Application Decisions



FDASIA 705: Risk-based Inspection

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.

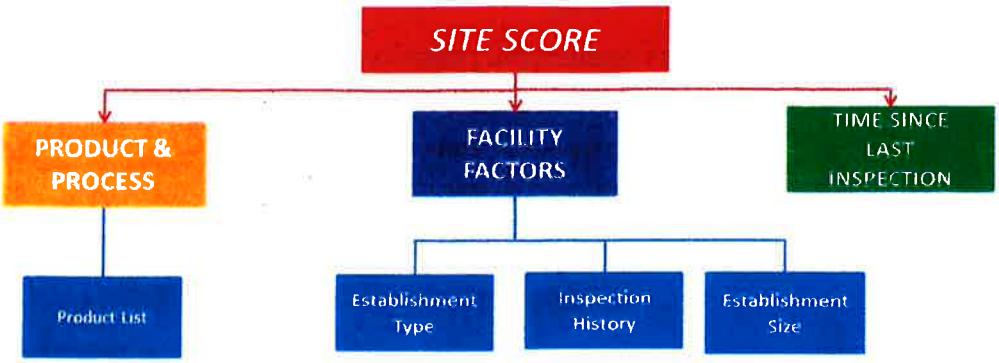
(C) The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment.

(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")

Site Surveillance Model → SSI List

- SSM reviewed annually per policy/procedure
  - Annual factors and weights documented
    - Reviewed and endorsed by CDER and ORA executive management
- Entire inventory processed through SSM annually
  - Excluding OAI firms (separated out for follow up by Office of Compliance)
  - Approximately 8K facilities in surveillance inventory
    - Not all segments are equal in terms of risk
      - Medicated shampoo vs. oral vs. sterile
  - ORA capacity for GMP/SSI inspections approximately 1700/year

What happens after SSI?

- Investigator closes inspection on site and issues 483 to firm if warranted
- Inspection package sent to Center for review
  - 483, EIR, firm's response
- OPQ/OS reviews package and completes classification (10 day goal) *
  - Refer to OC for enforcement action
  - Reclassify based on various factors (e.g., firm's response)
  - Other engagement (untitled letter, regulatory meeting, RAI letter)
- Next steps
  - If inspection closed out as NAI or VAI, final redacted EIR is issued to facility
  - If OAI, OC pursues enforcement action and manages remediation
    - Time to reinspection driven by facility readiness

* For domestic OAIs and all foreign

Moving Forward

- Refinement of process continues…
  - Increased communication within CDER and between CDER and ORA to increase awareness of application timing when a surveillance inspection has been separately requested (as output of the site surveillance model)
  - Improving our decision-making processes to ensure that non-OAI facilities are not blocking approvals (resolving potential OAIs more quickly)
  - ORA PAG more specialized group.
  - CDER reorganization
- Goal to further increase speed and transparency

FUTURE STATE FOR FACILITY ASSESSMENT AND INSPECTIONS

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NIPP
(NEW INSPECTION PROTOCOL PROJECT)

Grace McNally, Co-chair of NIPP/SIS
CDER/OPQ/Office of Process and Facilities

Vision for 21st Century Manufacturing

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight."

-- Dr. Janet Woodcock (October 2005)

Are we there yet?

New Inspection Protocol – Objectives

- What is the recipe for a successful inspection, one that adds value and encourages manufacturing quality?
  - Inspections should yield semi-quantitative assessments on the manufacturing quality at inspected facilities.
  - While continuing to document observed deficiencies, inspections should also identify practices that exceed basic compliance.
  - CDER and ORA collaborate through team-based inspections that include real-time sharing of findings and feedback.

Purpose of NIPP

- The inspection process focuses on measuring and describing the state of quality in the inspected facility.
- The inspection includes analyzable assessments to track and improve performance.
- Inspections identify excellence in manufacturing
- Knowledge from inspections will inform CDER decision-making, possibly including: site selection, industry outreach/training on positive manufacturing behaviors.

Overall Approach

- NIPP is designed to be a risk-and rule-based process using expert questions and a standardized inspection approach
- Two subgroups:
  - Pre-Approval Inspection (PAI)
  - Surveillance Inspection
- Sets of expert questions developed and approach currently being piloted
  - In parallel with, not in place of, normal inspection procedures
  - Not being used for compliance actions

PAI – Elements of an Inspection

- Multiple performance levels ranging from poor performance to exceeding basic compliance
- Concept - "confidence in commercial manufacturing"
- The three PAI objectives:
  - Readiness for Commercial Manufacturing
  - Conformance to application
  - Data integrity
- In addition to coverage described in the existing Pre-Approval Inspection Program (CP 7346.832), new areas assessed under the pilot include:
  - quality culture
  - maturity of the process development program
  - lifecycle risk management and oversight

Surveillance Inspection – Elements of an Inspection

- High-level subtopics within each of the six systems
  - Quality system
  - Facilities and equipment
  - Materials
  - Production
  - Packaging and labeling
  - Laboratory
- Initial focus on compliance program 56002A – Sterile Drug Process Inspections
- Scoring will be performed at the Element level
- For the six systems, 29 Elements were developed

Performance Levels

- Six performance levels (1-6)
  - Three levels of failure (critical, major, minor)
  - One acceptable level
  - Two levels of exceeding basic compliance
- These scores are applied to each Element
- Harmonized between PAI and Surveillance
- Performance is determined by CGMP compliance/violation, product impacts, and good practices that exceed CGMPs.

Next Steps

- Train investigators for pilot inspections
- Conduct inspections and evaluate outcomes
- Make improvements to NIPP protocols
- Expand surveillance protocol to other dosage forms

PROGRAM ALIGNMENT

Alonza Cruse
Pharmaceutical Quality Program Director
ORA, Office of Operations

ORA Program Alignment efforts...

- Transition to Commodity-Based and Vertically Integrated Regulatory Programs
- Training
- Work planning (Resource planning)
- Compliance Policy & Enforcement Strategy
- Imports
- Laboratories
- Information Technology

Action Plan Highlights:

Transition to Commodity-Based and Vertically Integrated Regulatory Programs

Developed a set of underlying sub-specialization categories in the pharma program.

Establishing joint cadre of compliance officers whose ultimate functions will include domestic & foreign activities.

Established a process for the joint development of course curriculum

Action Plan Highlights:

Training, Recruitment, Employee Skill and Career Enhancement

Create Specialized Investigators, Compliance Officers and First-line Managers

FDA will expand our level of specialized investigators, compliance officers and 1st line managers

ORA, especially in the pharma program, is looking at how we recruit, hire & develop staff.

Action Plan Highlights:
Agency Resource Planning

Developed a work-plan dashboard.

Establishment of one risk-based site selection model for surveillance inspections (foreign & domestic)

Action Plan Highlights:
Compliance Policy and Enforcement Strategy

Developing performance based public health metrics for compliance / quality activities

FDA is working towards a more team based approach across all components within the pharmaceutical program. Including application review ,inspections, compliance & enforcement. A couple of pilots currently underway...

Thank you for your attention!