Risk Based Pre-Approval Inspection

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Outline

• Background on Pre-Approval Inspections (PAIs)
• Risk based decision making related to PAIs
• Integrated Quality Assessment and PAIs
• New Inspection Protocol Project (NIPP)
• Future Directions
Background on Pre-Approval Inspections (PAIs)
A pre-approval inspection (PAI) is performed to contribute to FDA’s assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete.
Drug PAI Program Coverage

• Submission types:
  – Original ANDA, NDA, BLA submissions
  – CMC amendments to pending original submissions
  – CMC supplements to approved drug applications
  – Active pharmaceutical ingredients associated with a submission, including those in drug master files (DMFs)
  – Investigational New Drugs (rare)

• All facilities associated with a submission, domestic and international
Drug PAI Main Objectives

Objective 1: Readiness for Commercial Manufacturing
  a. Manufacturing and laboratory changes, deviations, and trends adequately evaluated
  b. Sound and appropriate sampling and testing program
  c. Contamination controls in place
  d. Adequate procedures for batch release, change control, investigating failures, deviations, complaints, and adverse events, etc.
  e. Feasibility of the proposed commercial process

Objective 2: Conformance to Application

Objective 3: Data Integrity Audit
Drug PAI Process in Brief

CDER determines need for inspection

District reviews and concurs with inspection request or waives the inspection

Pre-Approval inspection conducted, if warranted

Inspection report prepared & reviewed

Facility recommendation (Approve, Withhold)
Risk Based Decisions for Pre-Approval Inspections

- Determination of the need to for pre-approval inspection
- Determine areas for inspectional focus
- Evaluation of risks during inspection
- Post-inspection evaluation of inspection report

Approaches being Developed:
- Integrated Quality Assessment (IQA)
- New Inspection Protocol Project (NIPP)
Risk in Review and Inspection

• The concept of risk assessment in review and inspection is not new
• FDA has always used risk as part of regulatory decision making process
• Efforts are ongoing to standardize and formalize risk evaluation efforts to benefit:
  – Consistent regulatory decision making
  – Best utilization of resources
  – Greatest knowledge retention and sharing
Risk-Based Inspectional Philosophy

- Standardized and quantitative approaches, leading to standardized outcomes, related to quality
- Inspections will include additional site specific information
- Efficient and effective data gathering
- Identification of most meaningful risks to quality
- Decisions made from best relevant information
- Development of complete picture of facility performance

Maximizing the value of each inspection
Risk-Based Determination of Need for PAI
Team-based Integrated Quality Assessment (IQA)

- The Office of Pharmaceutical Quality (OPQ) will use a team-based Integrated Quality Assessment (IQA) approach to:
  - Maximize each team member’s expertise
  - Provide aligned patient-focused and risk-based drug product quality recommendations, inclusive of drug substance, drug product, manufacturing, and facilities
Integrated Quality Assessment (IQA) Team

Applications Technical Lead
Regulatory Business Project Manager

- **API**
  - ONDP
  - Division of Lifecycle API

- **Product**
  - OLDP
  - Product Divisions

- **Microbiology**
  - OPF
  - Division of Microbiology

- **Facility**
  - OPF
  - Division of Inspectional Assessment

- **Manufacturing, process, controls**
  - OPF
  - Division of Process Assessment

- **Dissolution**
  - ONDP
  - Division of Biopharm

**Facility Inspection**
ORA
Investigators
District Offices

**One Quality Voice!**
So, who makes the decision to request an inspection?

• For applications following the IQA process:
  – The facility reviewer makes the initial assessment of the need for inspection
  – All team members have an opportunity to provide input into the need for inspection
  – Any team member may request participation on the PAI
  – The district office or ORA HQ may modify the request
Determining Need for Inspection – Traditional Approach (CPGM 7346.832)

- **Priority Inspection Categories**
  - Establishment’s first time named in an application
  - First application by an applicant
  - First generic or New Molecular Entity (NME)
  - Narrow content assay range or titrated dosing
  - Substantially different manufacturing process than previously covered
  - API derivation is high risk or significant change in intended use
  - Numerous applications or other changes that may pose significant challenges to a firm’s state of control
  - Time since last inspection (a.k.a. 2/3/4 rule)

- **Discretionary Inspection Criteria**
  - Significant deficiencies during previous inspections
  - Other situations not previously described
  - District decisions
Determining the Need for a PAI (Evolving Approach)

- **Facility Risk:**
  Are there manufacturing risks associated with the inspectional history and current operations at this facility that impact the application?

- **Process Risk:**
  What are the manufacturing risks associated with the proposed unit operations in this application?

- **Product Risk:**
  Is there limited knowledge about the manufacture of this product? What’s the connection between manufacturing with clinical efficacy and patient safety?
Communicating Risk
Communicating Risks to the Inspection Team

• ORA* is part of the review team from early in the application process

• Information can be conveyed to the inspection team:
  – Written or verbal communication
  – Directly through IQA reviewer participation
  – Before, during and after inspection

• Information can be conveyed from the inspection team to the review team in similar ways
  – Communication during inspection to resolve overlapping quality assessment/cGMP issues

* NOTE: PAI/PLIs for BLAs are typically led by CDER.
Risk-Informed Communications – Some Best Practices

• Enhanced interdisciplinary communication throughout the review process
  – Proactive and collaborative conversations with all key players present
• Include known risks and potential unknown risks to quality
• Early discussion of potential risk mitigation strategies
• Recommendations and rationale that are clear to all team members
• End goal is an integrated product quality assessment (including facility information) that capture important links between product quality and patient outcomes
Seamless integration of review & inspection

One Quality Voice!
Conducting Risk-Based PAIs
New Inspection Protocol Project (NIPP): Goal

• To develop a new paradigm for inspections and reports that will advance pharmaceutical quality, including:
  – Standardized approach to inspection
  – Data gathering to inform “quality intelligence” of sites and products
  – Risk based and rule based process, using expert questions
  – Semi-quantitative scoring to allow for comparisons within and between sites
  – More common inspection report structure
  – Recognition of positive behaviors in cases where facilities exceed basic compliance
NIPP Organization Schematic

New Inspection Protocols
Project
Steering Committee

Pre-Approval Inspection Protocol(s) Subgroup

Observations to inform premarket review decisions

Surveillance Inspection Protocol(s) Subgroup

Observations on state of quality in a facility to assess quality risk

For Cause Inspection Protocol(s) Subgroup

Evidence of cGMP violations to support enforcement

Name TBD
PAI NIPP Approach

• Develop an expert question based template to evaluate quality and associated risk factors
• Include current PAI program objectives and additional elements related to quality culture
• Define performance levels, including levels exceeding basic compliance
• Include analyzable assessments (semi-quantitative scoring) that can track performance
• Provide an automated or semi-automated production of inspection reports with a common, searchable format (future work)
NIPP Expected Outcomes for FDA

• Maximize the value of time and resources spent on inspections
• Provide more consistent inspectional coverage and observations
• Facilitate faster and more consistent review of inspection reports
• Provide easily analyzable inspection data for trending, within and between sites
• Produce an assessment of the relative state of quality assurance of the firm being inspected (both positive and negative)
• Provide a tool to help determine the future inspection frequency based on risk
NIPP Expected Outcomes for Industry

• Provide more consistent inspectional coverage and observations
• Help provide clarity of expectations for industry practices
• Provide a benefit (e.g., reduced inspection frequency) for firms with high levels of manufacturing quality and performance
• Recognize and reward positive behaviors in cases where facilities exceed basic compliance
Status of PAI NIPP

• Phase I evaluation of PAI NIPP is near completion
  – Exploratory phase for feasibility
  – Includes 10 pre-approval inspections, now complete
  – Protocol only used for pilot purposes, and not factored into regulatory decision making or classification

• Preliminary results
  – Investigators liked it!
  – Great tool for inspection planning
  – Valuable recommendations made for ease of use and content

• Next steps
  – Collect and compile data related to completed inspections
  – Revise protocols, as appropriate
  – Plan for further piloting in 2016
Future Directions for PAIs

• CDER is committed to using risk based inspectional approaches!
• Continue cross-training OPQ staff to develop expertise for participating on inspection
• Further development of risk-based PAI selection model
• Refine communication between review & inspections
• Continue development and implementation of the New Inspection Protocol Project
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Please send questions or comments to:
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