Pre-Approval Inspection Program Update

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FDA/CDER/OPQ

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Objectives of Office of Pharmaceutical Quality (OPQ)

• A single unit in CDER dedicated to drug product quality
  – Across all drug product areas
    • new drugs, generic drugs, biotechnology products, and over-the-counter drugs
  – Across all sites of manufacture
    • domestic and foreign
Objectives of OPQ

• The creation of ‘one quality voice’ streamlining quality oversight throughout the lifecycle of a drug product
  – Aligns review, inspection, and research functional areas
  – Spans pre- and post-approval for brand and generic drugs
  – Strengthens surveillance and inspections of facilities globally
How OPQ was formed?

OGD

Chemistry and Micro

ONDQA → OBP → OTR → OPS

OC

preapproval and surveillance

OPQ
What is OPF?

The Office of Process and Facilities is:

- A large, diverse organization
  - Staffed by chemists (all types), pharmaceutical scientists, engineers, microbiologists, biologists, and others
- Responsible for a wide range of process related review and inspection aspects
  - Process review
  - Microbiology review
  - Preapproval inspection oversight
- Involved in nearly all application types
  - All original NDAs, ANDAs and BLAs
  - All site change sNDA, sANDA and sBLA
  - Certain complex drug substances
  - Some INDs, meeting packages, process change supplements
Office of Process and Facilities:

- OPF ensures that quality is built into manufacturing processes and facilities over the product lifecycle.
- OPF will use risk-based approaches for efficient assessment of the following application-related aspects:
  - Manufacturing facilities, processes, and controls for certain drug substances and intermediates, and for all ANDA and NDA drug products.
  - Microbiological aspects for drug substances and drug products.
  - Facility and manufacturing process suitability for commercial manufacturing and consistency with the principles of CGMP.
- Additionally, OPF partners with other offices internal and external to OPQ to establish standards for OPF-related review and inspectional activities.
## Inspection and Review – Pre-OPQ:

<table>
<thead>
<tr>
<th>Function</th>
<th>OGD</th>
<th>ONDQA</th>
<th>OPS-Micro</th>
<th>ORA</th>
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<td>Review Team</td>
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<td>ANDA Review (CMC/Micro)</td>
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<td>Request Inspection</td>
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<td>Perform Inspection</td>
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<td>Recommendation Post Inspection</td>
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### Inspection and Review – Post-OPQ:

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<thead>
<tr>
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<th>OLDP</th>
<th>ONDP</th>
<th>ORA</th>
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<td>x</td>
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<tr>
<td>ANDA Review (Process/Facility/Micro)</td>
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<td>NDA Review (Process/Facility/Micro)</td>
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<td>NDA Review (Micro)</td>
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<tr>
<td>Drug Substance Review (NDA)</td>
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<tr>
<td>Drug Substance Review (ANDA)</td>
<td>x*</td>
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<tr>
<td>Request PAI Inspection</td>
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<td>Perform PAI Inspection</td>
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<td>Recommendation for PAI After Inspection</td>
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</table>

x* = complex drug substance review
Benefits of Integrated Review and Inspection:

• Fully informed risk-based decision making related to quality
• Unified voice within FDA regarding quality
• Benefit to review, as reviewer better understands the implementation of the process and controls
• Benefit to inspection, as reviewer contributes their knowledge and expertise of review process
• Unified voice from inspection and review functions
• Enhanced risk-based decision making related to quality
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
- 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
- Prevent poor quality products from reaching market
PAI determination – Old Model

• Facility reviewer performs a site compliance evaluation to determine if a PAI should be performed using:
  - PAI triggers
  - Profile evaluation
  - Related profile to those previously inspected
  - Compliance status
  - Time since last inspection
  - Input from review team and ORA
Priority Pre-Approval Inspections: Risk Based Approach

- **Triggers for PAI Inspection:**
  - First time in an application?
  - First application filed by an applicant?
  - First generic application?
  - New Molecular Entity?
  - Narrow therapeutic index or titrated dosing?
  - History is unacceptable or not recently updated?
  - Substantially different process than previously covered at facility?
  - Product/process is high risk (API derived from animal tissue) or intended use has changed (API for non-sterile drug product (DP) to sterile DP)?
  - Certain site/process/product changes that are expected to pose significant challenge to the state of control? Numerous submissions?
Quality Considerations: Inspection(s):

Decision to Initiate Inspection:

- **Facility Risk**: What are the risks associated with the inspectional history for this facility, the capabilities of the facility, and current operations that impact the state of control for this facility?

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

- **Product Risk**: What product risks are associated with this formulation or dosage form? What is the connection between manufacturing and clinical efficacy and patient safety?
Pre-Approval vs. Surveillance Insp.: 

• While surveillance inspection of manufacturing sites often cover:
  - Products in distribution
  - Quality systems
  - Actual conditions and practices
  - Analytical methods
  - Ongoing state of control over processes and operations
  - Data integrity (information maintained on the site)
Pre-Approval vs. Surveillance Insp.:

- Pre-Approval inspections often cover more – such as an evaluation of:
  - Product development documentation
  - Bio/clinical batch manufacturing
  - Proposed manufacturing process, operational procedures, and batch records
  - Analytical method development
  - Data integrity (supporting application)
Objectives of Preapproval Inspection Program (CPGM 7346.832):

• Assure applications are not approved if the applicant has not demonstrated ability to operate with integrity and in compliance with CGMPs

• Assure:
  1. Readiness for manufacturing
  2. Adherence to application commitments
  3. Authenticity and accuracy of data submitted in applications

Negative findings can result in non-approval of application.
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 (cont.) (based on actual inspections)

- Identify firms not capable of manufacturing products, for example:
  - Equipment not installed
  - No quality agreement between sponsor and contract manufacturer listed in application
  - Lack of appropriate controls to ensure quality
  - Multiple batch failures not reported in application
Focus on During Internal/External Audits and Mock Inspections?

• Quality systems approach
• Data integrity issues
• Readiness for manufacturing
• Conformance to application commitments
• Contract manufacturers, API manufacturers, testing laboratories
# CGMP Inspection Classifications:

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<tr>
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<th>Marketed Product</th>
<th>Follow-up for FDA</th>
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<tbody>
<tr>
<td><strong>NAI</strong></td>
<td>Approval Rec., no 483</td>
<td>No 483</td>
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<tr>
<td><strong>VAI</strong></td>
<td>Approval Rec., 483</td>
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<tr>
<td><strong>OAI</strong></td>
<td>Withhold Rec., 483</td>
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- **NAI:** No action indicated
- **VAI:** Voluntary action indicated (e.g., 483)
- **OAI:** Official Action Indicated (e.g., 483 plus recommended action)
Post-Inspection Follow-Up:

• PAI initial recommendation by District Office
• Completion of Establishment Inspection Report (EIR)
• Evaluation of PAI EIR and firm 483 response within OPQ to make final recommendation
• Feedback to application review committee regarding inspection findings
• Final recommendations to OGD for all facilities related to application made by OPF
• Inspection information factored into lifecycle management for facility, determine need for future inspections
OPF Role in PAI Oversight:

• Evaluate need for pre-approval inspection (PAI) for manufacturing sites for all original applications and certain supplements
• Communicate the risks related to process and facilities to IQA team, including investigators
• Facilitate coordination of inspection with application timelines
• Frequently participate on PAIs as subject matter experts
• Make final site recommendation (Acceptable, Withhold) based on investigation recommendation and data from the application
Conclusions:

• Integration of review and inspection functions
• Communication within review team regarding review and inspection issues
• Risk based approach to determine need for inspection
• Focus on pre-approval inspection during facility review
• CGMP compliance issues with inspection (surveillance or PAI) can impact product approvals
Questions: