An Overview of ORA and CDER’s New Concept of Operations for Drug Facility Inspections and Evaluations

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THE VISION:

“…A maximally efficient, agile, flexible, manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight”

- Dr. Janet Woodcock, Director, FDA CDER
2013 FDA Program Alignment Charge

“…modernize and strengthen the FDA workforce to improve public health response”
Goals and Impact of Program Alignment in Pharmaceutical Quality

• Address challenges of globalization, scientific innovation, product diversity and complexity, new legislative mandates and limited resources;

• Improve consistency, transparency and collaboration in FDA’s respective operations to promote one quality voice;

• Reduce uncertainty for stakeholders by providing timely and expected communication of inspectional findings and facility assessments;

• Reduce the time to issue advisory and enforcement actions;

• Eliminate redundant reviews in the classification of inspections and achieve parity of domestic and international facilities;

• Clarify roles and responsibilities and increase access to facility and decisional information.
Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations (ConOps)

BACKGROUND

• ConOps whitepaper – Issued August 2017

• CDER and ORA will work in a vertically-integrated, programmatically-aligned environment regarding application review, inspections, and compliance activities

• Applies to Pre- and Post-Approval, Surveillance, and For-Cause Inspections

• Outlines an operating model for facility evaluation and inspection for human drugs

• Began to implement in Fall of 2017

• Goal of implementation by Fall of 2018
The following offices played a significant role in the development of ConOps:

- **Center for Drug Evaluation and Research (CDER)**
  - **Office of Pharmaceutical Quality (OPQ)**
    - Office of Policy for Pharmaceutical Quality (OPPQ)
    - Office of Process and Facilities (OPF)
    - Office of Surveillance (OS)
  - **Office of Compliance (OC)**
    - Office of Manufacturing Quality (OMQ)

- **Office of Regulatory Affairs (ORA)**
  - Office of Operations
  - Office of Pharmaceutical Quality Operations
  - Office of Medical Products and Tobacco Operations
  - Office of Policy and Risk Management
ConOps Highlights

What is different?

- Improved communication with stakeholders
- Defined timelines,
  - 90-Day decisional letters
  - 6-month goal for enforcement actions
- Parity between domestic and international inspections
- See the ConOps Q&A at:
  https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm576309.htm

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TYPE OF INSPECTION: PRE-APPROVAL
Pre-Approval Facility Evaluations and Inspections directly support the assessment of marketing applications by:

- Ensuring that a named facility is capable of conforming with CGMP requirements
- Ensuring that data submitted in the application are accurate and complete

Pre-Approval Facility Evaluations are led by CDER with ORA participation

- Initiated in conjunction with the submission of a marketing application
- Considers available information about each facility named in a marketing application
- Determines whether a Pre-Approval Inspection is needed to support decision-making regarding the approvability of a marketing application from a quality perspective

Pre-Approval Inspections are led by ORA with CDER participation

- Inspection directly supports the assessment of marketing applications
- Evaluates the adequacy of the manufacturing processes and control strategy
- Ensures commercial product quality and conformance to application, facility, and CGMP requirements
- The inspection information is used in conjunction with other information to determine the overall approvability of a drug application
Pre-Approval Facility Evaluations and Inspections

Planning the Strategy for the Inspection

• At the time of submission, an Integrated Quality Assessment (IQA) Team is assembled to perform the quality assessment of a particular marketing application, led by OPQ

• IQA Team provides aligned, patient-focused, and risk-based drug product quality recommendations inclusive of drug substance, drug product, manufacturing, and facilities

• Unifying hallmark of IQA is the integration of the facility evaluation and inspection and review roles in the application assessment process

• ORA investigators are apprised of any issue uncovered by CDER reviewers, and vice versa

• IQA Team is ultimately responsible for providing the quality recommendation for marketing applications

• Includes the Pre-Approval Facility Evaluation and may also include a Pre-Approval inspection, in advance of the Biosimilar, Generic Drug, or Prescription Drug User Fee Acts goal dates

• If an on-site Pre-Approval Inspection is deemed necessary, the IQA Team, including the assigned ORA representative, identify areas of concern found during assessment of the application for inspectional coverage
Conducting the Inspection

- ORA investigator leads the inspection with participation from CDER, may focus in the areas of concern outlined by the IQA Team

- Inspection team conducts the site inspection by following the Pre-Approval Inspection Compliance Program and provides coverage to the areas of concern identified by the IQA Team

- Investigator, with input from the inspection team, documents objectionable findings and issues an FDA Form 483 when significant issues are identified
Communicating the Findings of the Inspection

- Inspection team provides the EIR to the IQA Team after it has been reviewed by the ORA Director of Investigations Branch (DIB) or designee.

- IQA Team, for Pre-Approval Inspections includes an ORA representative, evaluates the report.

- IQA may address any outstanding issues, through regulatory meetings or an Information Request (IR), Discipline Review (DR), or Complete Response (CR) letter, and provide an overall recommendation on approvability of the application.

- OPF assessor evaluates the sponsor’s or facility owner’s responses to questions in the IR/DR/CR and provides the final recommendation on the approvability of the application.

- IQA team provides an overall recommendation on approvability of the application following this assessment.

- **Timing will be driven by user fee deadlines**
TYPE OF INSPECTION: POST-APPROVAL
Post-Approval Facility Inspections

- Similar to Pre-Approval Facility Inspections – they are product specific but conducted after applications have been approved

- Inspections focus largely on the process validation lifecycle and any manufacturing changes that may have occurred following approval

- Changes in perceived risk may also initiate an inspection, even in cases where a Pre-Approval inspection was not deemed necessary

- Inspections are led by ORA with CDER participation

- Ensure that commercial-scale processes for an approved drug product conform to application commitments and CGMP requirements

- Inspection information is used to update lifecycle risk for a specific drug product or to determine any regulatory actions
Planning the Inspection

- IQA Team, or ORA in communication with the IQA Team, determines the need for a Post-Approval inspection after or as part of the review and approval of a marketing application.

- IQA Team captures potential risk in a lifecycle dashboard which informs the post-approval processes.

- OPF uses this lifecycle dashboard to assess residual risk or necessary follow-up and determine if a Post-Approval inspection is needed.

- If no inspection is needed, OS monitors and evaluates product quality.

- If a Post-Approval inspection is necessary, OPF prepares an assignment to provide suggested areas of concern during the inspection.
Conducting the Inspection

- Inspection team performs the inspection following the Post-Approval Compliance Program and provides coverage in the areas of concern.

- If the inspection team observes critical conditions, they are discussed with OPF, who will include OC and OS as needed, before the inspection closes.

- If deemed necessary, the inspection may expand to a Surveillance Inspection based on a Drug Manufacturing Inspections Compliance Program.

- Ultimately, the inspection team documents objectionable findings and issues an FDA Form 483 when it identifies significant CGMP issues.
Post-Approval Facility Inspections

Communicating the Findings of the Inspection

• When objectionable findings are observed, the investigator documents the findings, issues an FDA Form 483, and discusses it with the firm at the close of the inspection

• ORA completes the report and initial recommendation in 45 days post-inspection. OPF completes the final assessment and recommendation in the following 45 days

• OPF initiates follow-up action with the sponsor, site, and/or related programs (e.g., ORA, OS, OC) in the following 10 days, as needed

• Finally, OPF updates risk profile in the lifecycle dashboard with information gained from the inspection
TYPE OF INSPECTION:
SURVEILLANCE
Surveillance Facility Inspections

- Focus on facilities that manufacture marketed prescription and over-the-counter monograph drug products as well as in-process materials or drug substances used in marketed drug products
- Inspections monitor conformance to CGMP requirements, not necessarily an assessment of a specific product
- It is a system-based inspection
- Goal of the inspection is to identify quality problems and adverse trends so that the FDA can develop strategies to mitigate them
- ORA leads surveillance inspections with CDER participation, when requested by ORA
- ORA investigators carry out inspections at facilities identified by CDER’s surveillance risk model
Planning the Inspection

• OS develops and uses a risk-based site selection model to assess the relative quality risks for facilities in the manufacturing facility catalogue

• This model generates a risk-based ranking of sites to annually prioritize the highest risk facilities for inspection

• After a list of sites is identified, ORA schedules inspections for individual sites

• In advance of a scheduled inspection, OS prepares an up-to-date site dossier

• ORA conducts an on-site inspection based on the Surveillance Compliance Program and quality information summarized in the site dossier
Surveillance Facility Inspections

- Understanding CDER’s Risk-Based Site Selection Model; MAPP 5014.1

- Released 9/26/18 to create greater transparency around FDA’s site selection model

- Goal to ensure inspections are prioritized based on potential risks to patients, and use resources efficiently
Surveillance Facility Inspections

Risk Factors Identified in section 510 of FDCA:

• Compliance history
• Record, history and nature of recalls
• Inherent risk of the drug
• Inspection frequency and history
• Inspection history by foreign regulatory authorities
• Any other criteria determined by Secretary
Surveillance Facility Inspections

Risk Factors for Inclusion in the Site Selection Model:
• Site type (manufacturer, packager only, control lab only)
• Time since last surveillance inspection (or never inspected)
• FDA compliance history
• Foreign regulatory inspectional history
• Patient exposure
• Hazard signals (FARs, BPDRs, MedWatch reports, recalls, etc.)
• Inherent product risk
• Dosage Form
• Route of Administration
• Products intended to be sterile
• API load (concentration of API in dosage form or unit dose)
• Biologic drug substance or drug product
• Therapeutic class
• Narrow Therapeutic Index (NTI) drugs
• Emergency use drugs
Surveillance Facility Inspections

• OAI sites and sites on import alert are excluded from Site Surveillance Model

• Site re-inspection is determined instead as part of enforcement effort
Conducting the Inspection

- ORA and possibly CDER personnel perform the inspection
- If ORA observes critical conditions (e.g., they may result in an imminent health hazard), they may be discussed between ORA and OMQ before the inspection closes
- ORA or designee, the investigator(s), and OMQ collaboratively decide whether to continue the inspection to gather additional information or to close the inspection to initiate prompt regulatory action
Communicating the Findings of the Inspection

- When objectionable findings are observed, the investigator documents the findings, issues an FDA Form 483 and discusses it with the firm.

- ORA informs CDER as soon as practical, but at most within two days of closing the inspection, that a facility is potentially OAI.

- **Within 45 days of the close of a surveillance inspection, ORA completes the EIR, proposes a classification**
  - Official Action Indicated (OAI)
  - Voluntary Action Indicated (VAI)
  - No Action Indicated (NAI)
Surveillance Facility Inspections

**OAI Classification**

- Inspection indicates an initial OAI classification, ORA conducts an initial written classification analysis and refers the matter and documents to OMQ within 45 days of closing the inspection

- **OMQ determines a final classification and, subject to input from the Office of the Chief Counsel, issues a decisional letter in the following 45 days (90 days following the inspection closing)**

- OMQ, solely or in collaboration with ORA, takes appropriate action within 3 months of the decisional letter - OMQ and ORA collaborate on interactions with facilities

- OMQ determines that an enforcement action is not warranted, ORA is notified of the downgraded classification and provided a written description of the reason(s) for downgrade within 40 days

- OC will then issue an FMD-145/decisional letter no later than 90 days following the inspection closing. OS is notified of the downgrade for trending purposes

**NAI / VAI Classification**

- Inspection receives an NAI or VAI classification and no further action is recommended, ORA issues an FMD-145/decisional letter within 90 days following the inspection closing
Surveillance Facility Inspections

Post-Inspection Surveillance Analysis

• OS conducts post-classification analysis of relevant quality information available to examine trends in quality issues observed across firms, products, regions, etc.

• OS uses this trending analysis to identify a sub-set of firms (e.g., firms with OAI reclassified to VAI) for follow-up engagement

• OS and ORA collaborate on the engagement with this sub-set of firms to address negative or concerning quality trends
TYPE OF INSPECTION: 
FOR-CAUSE
For-Cause Inspections

For-Cause Facility Inspections

- Initiated in response to a new registrant or a specific event or information that brings into question the compliance and/or quality of a manufacturing practice, facility, process, or drug.

- Inspection is meant to gather additional information to determine the quality of marketed product and whether enforcement actions are warranted.

- Inspections may also be used to investigate compliance with sponsor obligations and to follow-up to verify corrective actions following enforcement actions.

- ORA leads for-cause inspections with CDER participation when appropriate.

- For-cause inspections identified by ORA, CDER or other sources.

- For-cause inspections can focus on specific issues and evaluate a firm’s conformance to CGMPs.
For-Cause Inspections

Planning the Inspection

• Requests for For-Cause Inspections can be initiated by ORA, OPF, OS, or OC as the result of a specific event or information that bring into question the compliance and quality of a manufacturing practice, facility, process, or drug

• Inspection assignments intended to cover other program areas (e.g., unapproved drug and bioresearch monitoring inspections), not covered by this operating model

• Once an inspection is warranted, the office prepares an assignment that sets forth the areas of required coverage and/or refers to a Drug Manufacturing Inspections Compliance Program

• Once the assignment is approved, ORA schedules the inspection, dependent on risk and priorities

• ORA, and possibly CDER, performs the on-site inspection, though CDER may participate, as requested

• Inspection team develops an on-site inspection strategy based on the coverage requirements contained in the assignment
For-Cause Inspections

Conducting the Inspection

• Inspection team conducts the inspection following the assignment

• If major deficiencies are uncovered, the inspection team discusses findings with the initiating office and involves other offices (e.g., OPF, OS, OC), as appropriate

• Collectively, they will discuss whether to continue the inspection to gather additional information or to close the inspection and initiate prompt regulatory action
For-Cause Inspections

Communicating the Findings of the Inspection

• If objectionable conditions are observed, the investigator issues an FDA Form 483 and discusses it with the firm

• Within 45 days of the close of the inspection, ORA completes an EIR

• Initiating office completes a final assessment or classification in the following 45 days, involving other offices (e.g., ORA, OPF, OS, OC) as appropriate

• **Any follow-up actions are completed within 6 months of the inspection**

• Finally, OS updates the site dossier for the facility with information gained from the inspection
90-Day NAI Decisional Letter

Based on this inspection, this facility is considered to be in an acceptable state of compliance…"
90-Day VAI Decisional Letter

September 18, 2018

Mr. Jane Smith
President
Good Quality Drugs
City, State

Dear Dr. Smith:

The U.S. Food and Drug Administration (FDA) conducted an inspection at Good Quality Drugs, Firm 12345678, located at City, State, from May 7, 2018, to May 11, 2018. FDA has determined that the inspection classification of this facility is “voluntary action indicated” (VAI). Based on this inspection, this facility is considered to be in a minimally acceptable state of compliance with regard to current good manufacturing practice (CGMP).

A VAI inspection classification indicates that, although investigators found and documented objectionable conditions during the inspection, FDA will not take or recommend regulatory or enforcement action because the objectionable conditions do not meet the threshold for action at this time. Despite this facility inspection classification, FDA recommends that you address the observations noted on the Form FDA 483 issued at the conclusion of the inspection or otherwise conveyed to you following the inspection. If not corrected, the same or similar conditions could lead to a future inspection being classified as “official action indicated” (OAI).

This letter is not intended as an endorsement or certification of the facility. It remains your responsibility to ensure continued compliance with CGMP.

An inspection classification of VAI for CGMP compliance will not directly negatively impact FDA’s assessment of any pending marketing applications referencing this facility. Please note, however, that application approval will depend on a product- and application-specific facility assessment conducted by the appropriate CDER review office. This letter does not address or reflect FDA’s decision making with respect to any potential non-CGMP compliance issues.

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“Based on this inspection, this facility is considered to be in a minimally acceptable state of compliance…”
“Based on this inspection, this facility is considered to be in an unacceptable state of compliance…”
Thank You!