



# **An Overview of ORA and CDER's New Concept of Operations for Drug Facility Inspections and Evaluations**

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## THE VISION:

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*“...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 implementation in Fall of 2017

# Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations (ConOps)

## Background (cont.)

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)
  - **Now the Office of Pharmaceutical Manufacturing Assessment (OPMA)**
- Office of Surveillance (OS)
  - **Now the Office of Quality Surveillance (OQS)**

- **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 timeliness,
  - 90-Day decisional letter
    - [OAI 90-Day decisional letter](#)
    - [VAI 90-day decisional letter](#)
    - [NAI 90-day decisional letter](#)
  - 6-month goal for enforcement actions
- Parity between domestic and international inspections
- See the ConOps Q&A at: <https://www.fda.gov/drugs/pharmaceutical-quality-resources/questions-and-answers-integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept>

# The 90-Day Letter

## Goal

- Increase engagement with industry by communicating the final inspection classification to the facility within 90 days of the end of the inspection

## Scope

- Applies to any surveillance inspection
- Includes “NAI” (No Action Indicated), “VAI” (Voluntary Action Indicated), and “OAI” (Official Action Indicated) letters

## GDUFA and ConOps

- The 90-Day Letter was created to meet GDUFA II commitment and to achieve ConOps communication goals



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**TYPE OF INSPECTION:**  
***PRE-APPROVAL***

# Pre-Approval Facility Evaluations and Inspections

**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 issues 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**

# Pre-Approval Facility Evaluations and Inspections

## 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



# Pre-Approval Facility Evaluations and Inspections

## 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**

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**TYPE OF INSPECTION:**  
***POST-APPROVAL***

# Post-Approval Facility Inspections

## 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**

# Post-Approval Facility Inspections

## 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**



# Post-Approval Facility Inspections

## 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

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**TYPE OF INSPECTION:**  
***SURVEILLANCE***

# Surveillance Facility Inspections

## 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**

# Surveillance Facility Inspections

## 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

## Identifying Facilities for Surveillance 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
  - Outlines the risk factors FDA used in the Site Selection Model (SSM) to generate the Site Surveillance Inspection List that prioritizes sites for surveillance inspection
  - Higher risk sites are assigned to ORA for inspection that fiscal year
  - Goal is to achieve parity in inspection frequency for sites with equivalent risk (regardless of geography or product type) and use resources efficiently, or to ensure inspections are prioritized based on potential risks to patients
- **Risk factors consistent with Section 510 of FDCA**
- Annual review and approval process – CDER and ORA
  - Risk factors, weights, and methodology assessed, areas for improvement or modification identified

# 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 (MAPP 5014.1):

- 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



# Surveillance Facility Inspections

## 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

# Surveillance 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
- 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

# Surveillance Facility Inspections

## Sharing Inspection Outcomes—Inspection Classification Database

- Provides the most recent classifications of inspections of manufacturing facilities conducted for routine CGMP surveillance purposes or inspections of sites conducting bioequivalence/bioavailability studies
- Provides transparency to the industry, the general public, and other regulators
- Database also updated to build on FDA's progress implementing the Mutual Recognition Agreement (MRA) with the European Union
- Updated every 30 days

U.S. FOOD & DRUG ADMINISTRATION

Home / Inspections, Compliance, Enforcement, and Criminal Investigations / Inspection References / Inspection Classification Database

### Inspection Classification Database

Content current as of: 09/12/2018

**Important Note:**

- Not all inspections are included in the database. Inspections conducted by States, pre-approved inspections, mammography facility inspections, inspections waiting for a final enforcement action, and inspections of nonclinical labs are not included. Inspections of nonclinical labs are available at [Nonclinical Laboratories Inspected under Good Laboratory Practices](#).
- The results show final classifications of No Action Indicated (NAI), Voluntary Action Indicated (VAI), Official Action Indicated (OAI) for each product area within an inspection.

The Food and Drug Administration (FDA) conducts inspections of regulated facilities to determine a firm's compliance with applicable laws and regulations, such as the Food, Drug, and Cosmetic Act and related Acts.

FDA discloses a segment of inspection information to help improve the public's understanding of how the FDA works to protect the public health. Disclosure of a firm's inspection information encourages firm compliance and provides the public with an understanding of the Agency's enforcement actions and an ability to make more informed marketplace choices.

Some inspection data may not be posted until a final enforcement action is taken. This database does not represent a comprehensive listing of all conducted inspections and should not be used as a source to compile official data.

Inspection References

- Practice Safety Inspections
- Inspection Clusters
- Inspection Classification Database
- Inspection Observances
- FDA Outreach Response Field Guides
- Inspection Guides
- Investigations Operations Manual

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**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 – 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

# ConOps: Office of Compliance Progress Toward 6 Month Enforcement Actions

- From FY15 to FY19 there was an overall median 58% improvement while increasing Warning Letter issuance overall

2015	2016	2017	2018	2019
Inspection Report Received by CDER to WL Issued	Inspection Report Received by CDER to WL Issued	Inspection Report Received by CDER to WL Issued	Inspection Report Received by CDER to WL Issued	Inspection Report Received by CDER to WL Issued
10.8 months on average	8.6 months on average	5.7 months on average	5.3 months on average	4.4 months on average

- In FY19, OC reported a 94% success rate in meeting its goal of issuing OAI classification letters to facilities within 90 days from the close of inspection

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# Thank You!