FDA'S INSPECTION PROCESSES FOR HUMAN DRUGS ***WHAT SHOULD YOU ANTICIPATE?***

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IPA Advanced GMP Workshop 2018

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AGENDA

- **Overview - The Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations**
- **Types of Inspections**
  - Surveillance inspections
  - Pre-Approval Inspections
  - Post approval Inspections
  - For Cause Inspections
- **Other related topics**
  - Decisional Letters and Inspection Classification
  - Import Alerts
  - Inspection Database
- **Questions**

Notice: Information in these slides are from documents available on the U.S. FDA website and webpage links are provided throughout

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INTEGRATION OF FDA FACILITY EVALUATION AND INSPECTION PROGRAM FOR HUMAN DRUGS: A CONCEPT OF OPERATIONS (ConOps)

ConOps discusses how the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) will…

"…work in a vertically-integrated, programmatically-aligned environment regarding application review and inspections, and the compliance activities associated with them."

Published in June 2017

The ConOps applies to Pre-and Post-Approval, Surveillance, and For-Cause Inspections and…

"…outlines an operating model for facility evaluation and inspection for human drugs."

Information on "ConOps":
https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/UCM574362.pdf
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm576309.htm

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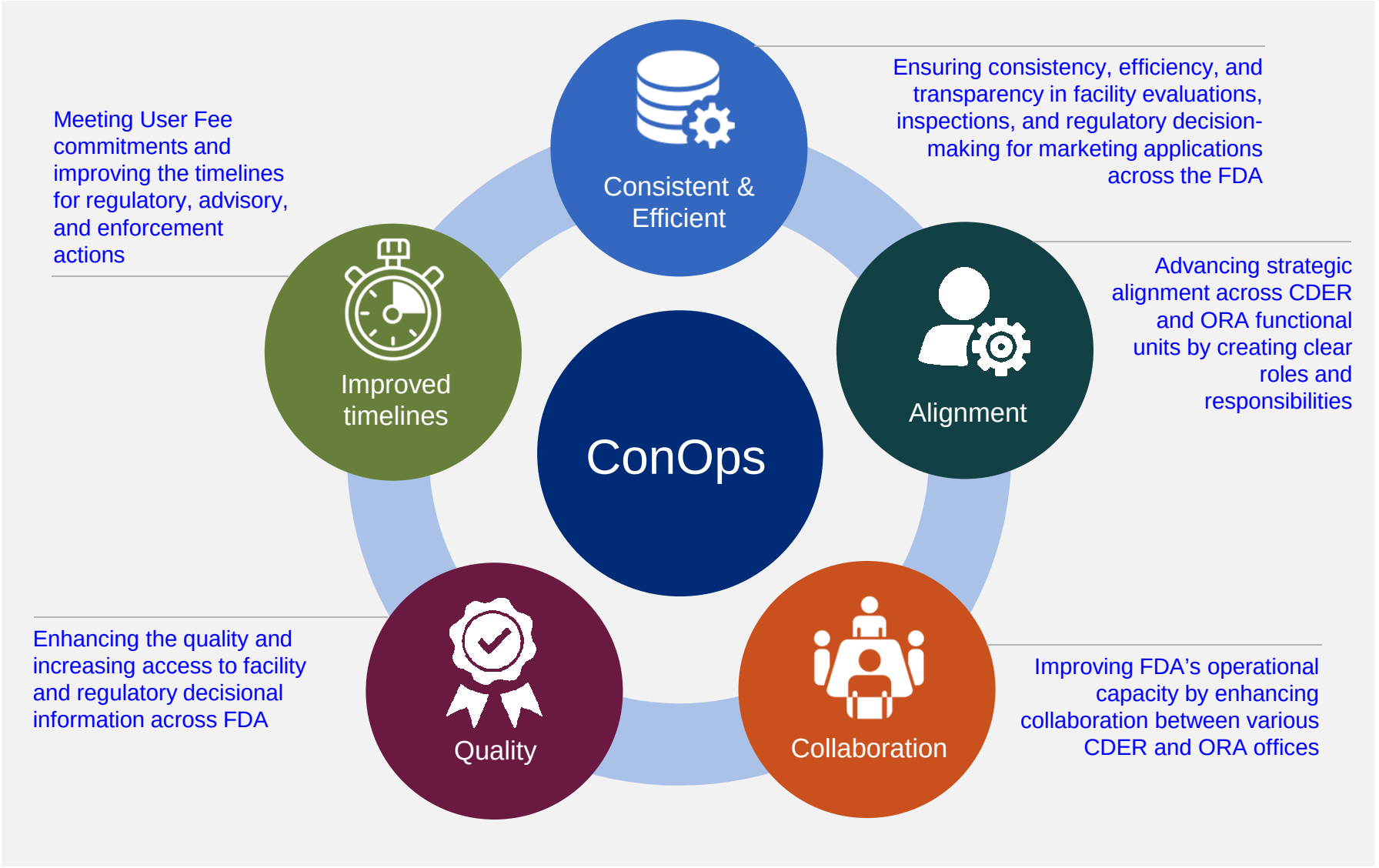
THE ConOps - WHY?



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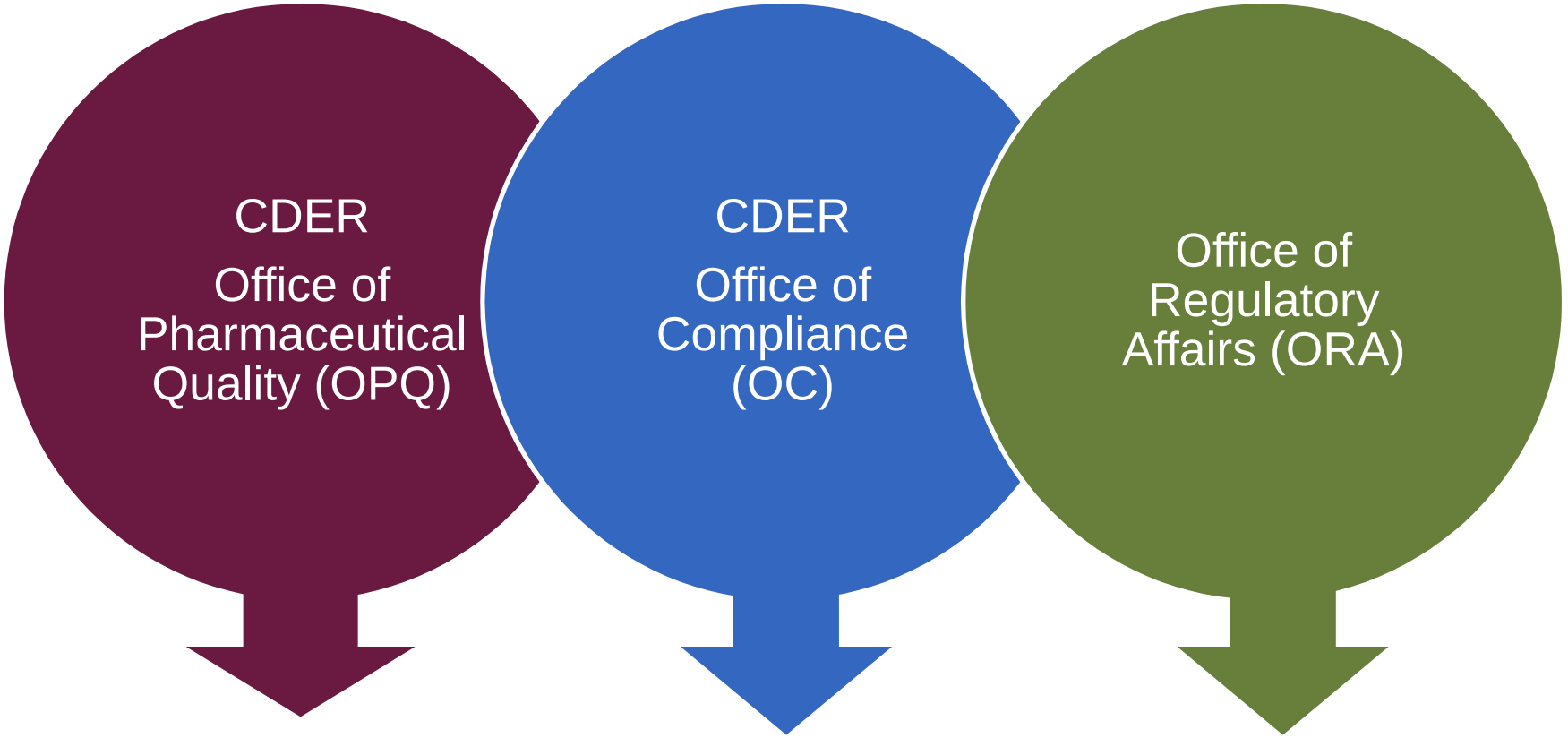
KEY GROUPS INCLUDED IN THE ConOps



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ConOps AND PROGRAM ALIGNMENT

ConOps

Complementary to the Program Alignment initiative

The Program Alignment initiative implements a program-based management structure that aligns staff by FDA-regulated product (e.g., Drugs, Devices, Biologics, etc.) and enhances the effectiveness of communications, processes, and ORA's ability to keep pace with scientific innovation and protect public health.

Information on Program Alignment:

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ucm549087.htm

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ConOps AND GDUFA II

Per the ConOps Q&A, the most anticipated results for the ConOps implementation are:

Meeting the Generic Drug User Fee Amendments II (GDUFA II) commitment to communicate Surveillance Inspection classifications to facility owners *within 90 days of the end of an inspection*

+

Meeting GDUFA or Prescription Drug User Fee Act (PDUFA) application timeframes for Pre-Approval Inspections

CDER and ORA began issuing the **90-day decisional** letters in late 2017 with a goal of **90 percent** in this timeframe in 2018

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ConOps AND CURRENT POLICIES & PROCEDURES

1. CDER and ORA began developing processes to begin to operationalize these workflows in the fall of 2017.

2. FDA has *begun updating* appropriate documents such as Compliance Programs (CPs, formerly known as Compliance Program Guidance Manuals), the Investigations Operations Manual (IOM), and the Regulatory Procedures Manual (RPM).

3. The Surveillance Inspection CP was updated in the fall of 2017.

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ConOps AND ISSUES AT FACILITIES

Manufacturers *are responsible* for ensuring that their products are manufactured to meet all of the quality standards and in accordance with the current good manufacturing practice (CGMP) regulations.

The ConOps promotes transparency and communication between the agency and industry for facilities involved in manufacturing human drugs

The enhanced communication between FDA and facility owners *may help* to address problems more efficiently.

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SURVEILLANCE

FACILITY INSPECTIONS

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SURVEILLANCE FACILITY INSPECTIONS

1. Surveillance Facility Inspections focus on facilities that manufacture *marketed prescription* and *over-the-counter drug products* as well as in-process materials or drug substances used in marketed drug products.
2. This type of inspection is *meant to monitor the conformance to CGMP requirements* and is not necessarily an assessment of a specific product.
3. It is a system-based inspection.
4. The purpose of this type of inspection is to identify quality problems and adverse trends at facilities so that the FDA can develop strategies to mitigate them.
5. ORA leads Surveillance Facility Inspections with CDER participation, when requested by ORA.
6. ORA investigators carry out Surveillance Inspections at facilities identified by CDER's *surveillance risk model*.

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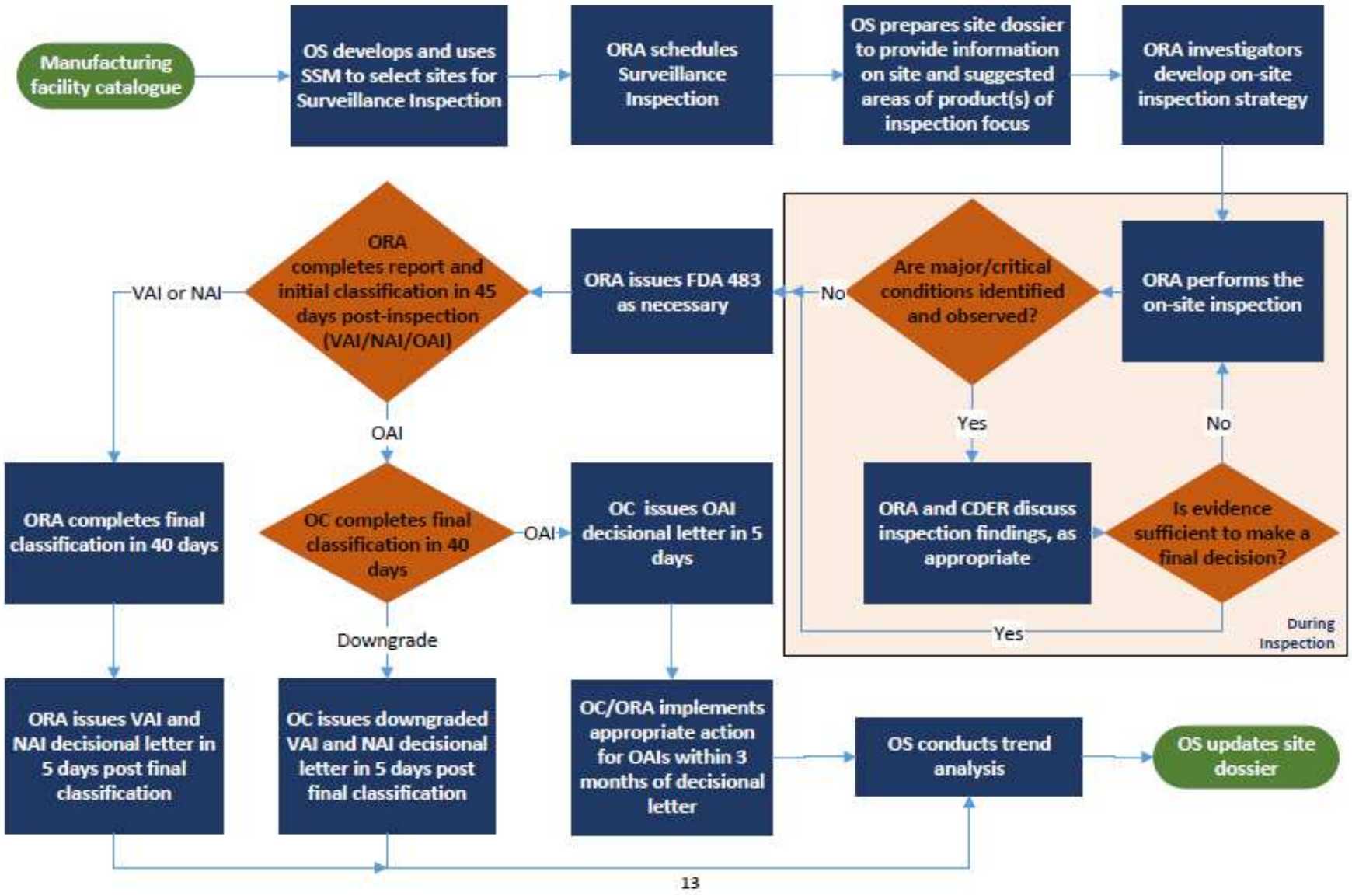
Surveillance Facility Inspection



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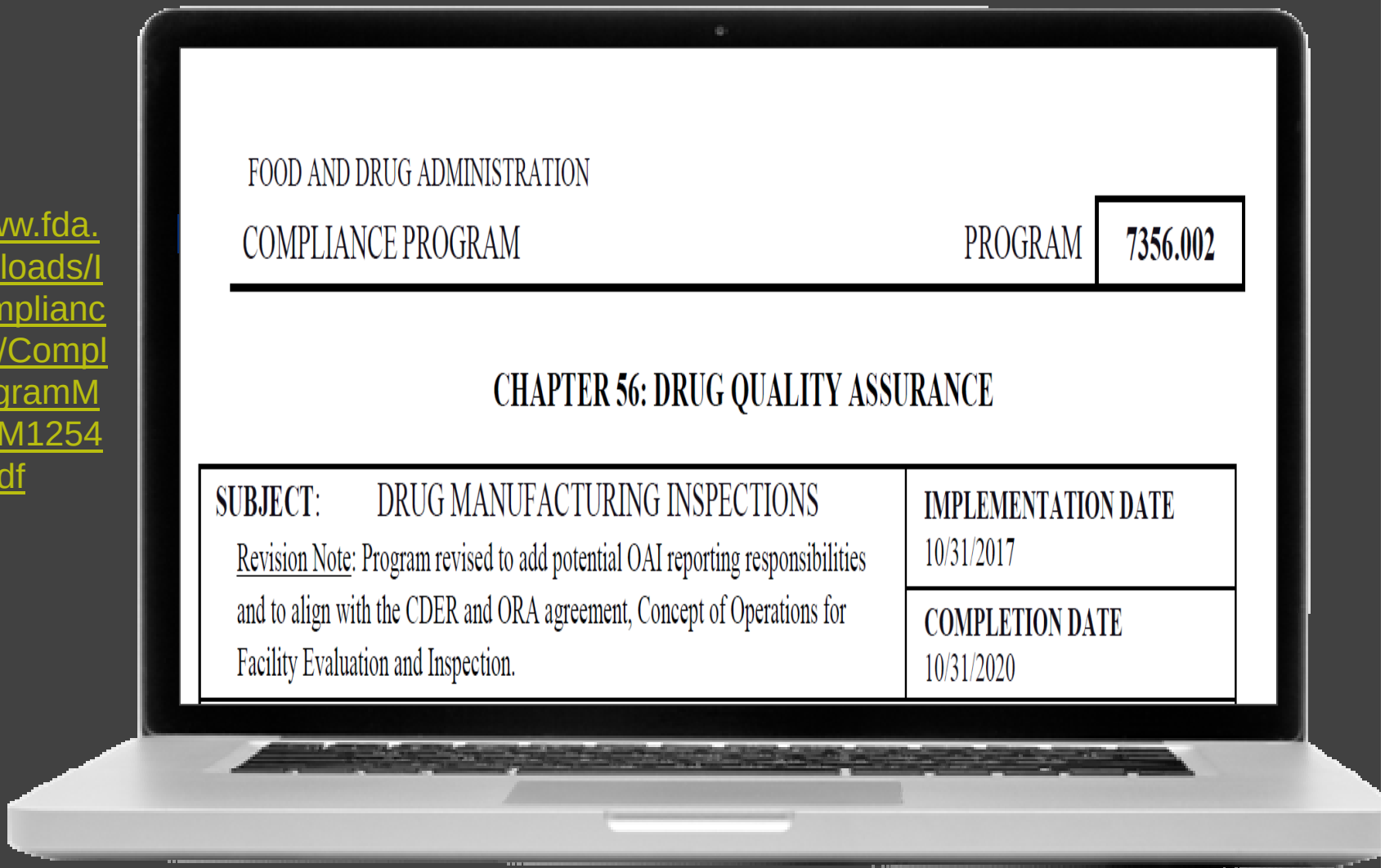
CPGM 7356.002 - UPDATED 10/31/2017 (1)

https://www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePrograMManual/UCM125404.pdf



FOOD AND DRUG ADMINISTRATION

COMPLIANCE PROGRAM | PROGRAM 7356.002

CHAPTER 56: DRUG QUALITY ASSURANCE

SUBJECT: DRUG MANUFACTURING INSPECTIONS

Revision Note: Program revised to add potential OAI reporting responsibilities and to align with the CDER and ORA agreement, Concept of Operations for Facility Evaluation and Inspection.

IMPLEMENTATION DATE
10/31/2017

COMPLETION DATE
10/31/2020

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CPGM 7356.002 - UPDATED 10/31/2017 (2)

Office of Regulatory Affairs (ORA)

Major changes in the 7356.002 compliance program are related to roles and responsibilities for surveillance inspections and timing of communications from FDA to inspected facilities are summarized

- Schedules surveillance inspections for individual sites and leads surveillance facility inspections with CDER participation, based on the CPGM and quality information summarized in a site dossier
- If the initial classification is Official Action Indicated (OAI) [**pOAI**], ORA provides a classification to the Office of Manufacturing Quality (OMQ) in CDER's Office of Compliance (OC) within *45 calendar days of closing the inspection*
- If the facility inspection results in an ORA recommendation for a No Action Indicated (NAI) or Voluntary Action Indicated (VAI) classification and no further action is recommended, ORA issues *a decisional letter* within 90 calendar days following the inspection closing

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Office of Manufacturing Quality (OMQ) in CDER's Office of Compliance (OC)

- Makes a final classification for pOAI cases, with input from the Office of the Chief Counsel, and issues a decisional letter in 90 calendar days following the inspection closing (e.g. *letter to a facility that they are OAI*)
- If an inspection is classified as OAI, OMQ, solely or in collaboration with ORA, takes an appropriate action within 90 calendar days of the decisional letter (e.g. *Warning Letter, import alert, regulatory meeting*)
- If an advisory or enforcement action is not warranted (i.e., *initial classification downgrade*), OMQ notifies ORA of the change in classification

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HOW DOES FDA COMMUNICATE THE FINAL INSPECTION CLASSIFICATION?

- The ConOps created 90-day facility classification decisional letters
- The letter is sent within 90 days from the end of an inspection
- There are separate letters used depending on the facility classifications:
  - no action indicated (NAI)
  - voluntary action indicated (VAI)
  - official action indicated (OAI)

90-day decisional letter

Explains what the classification means as well as how it may impact a company's application approval

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IMPORT ALERTS

https://www.fda.gov/ForIndustry/ImportProgram/ActionsEnforcement/ImportAlerts/default.htm#purpose

- Import alerts inform FDA field staff and the public that the agency has enough evidence to allow for Detention Without Physical Examination (DWPE) of products that appear to be in violation of FDA laws and regulations.

- These violations could be related to the product, manufacturer, shipper and/or other information.

What is the purpose of an Import Alert?

- Prevent potentially violative products from being distributed in the United States;
- Free-up agency resources to examine other shipments;
- Provide uniform coverage across the country;
- Place the responsibility back on the importer to ensure that the products being imported into the United States are in compliance with FDA laws and regulations.

- For information on how to be removed from an import alert, please see the import alert removal page.

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SITE SELECTION MODEL

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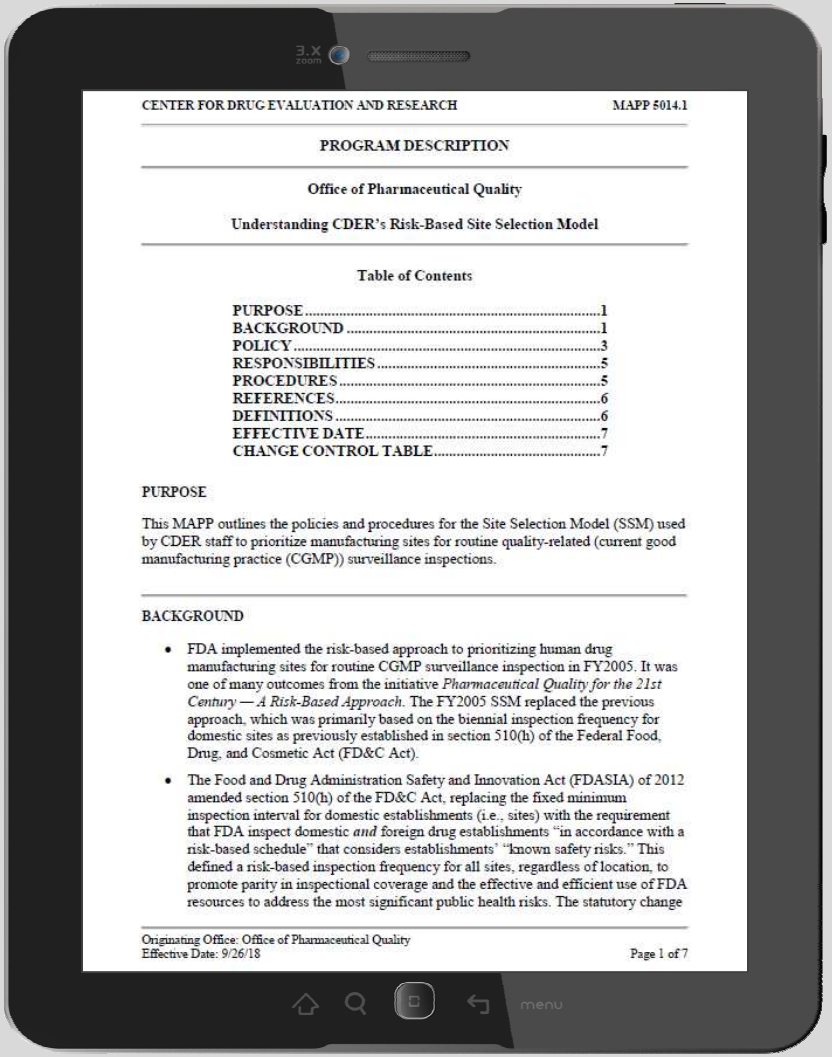
RISK BASED SITE SELECTION MODEL – MAPP 5014.1

- Office of Surveillance (OS) uses a risk-based site selection model to annually identify facilities for inspection, and prepares an up-to-date site dossier for each of the identified facilities in advance of a scheduled surveillance inspection
- OS will use the SSM to generate a risk score for each site. Scoring of risk components is based on either empirical evidence collected by FDA, subject matter experts' judgment, or a combination of both.

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM619302.pdf



CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5014.1

PROGRAM DESCRIPTION

Office of Pharmaceutical Quality

Understanding CDER's Risk-Based Site Selection Model

Table of Contents

PURPOSE

This MAPP outlines the policies and procedures for the Site Selection Model (SSM) used by CDER staff to prioritize manufacturing sites for routine quality-related (current good manufacturing practice (CGMP)) surveillance inspections.

BACKGROUND

- FDA implemented the risk-based approach to prioritizing human drug manufacturing sites for routine CGMP surveillance inspection in FY2005. It was one of many outcomes from the initiative *Pharmaceutical Quality for the 21st Century — A Risk-Based Approach*. The FY2005 SSM replaced the previous approach, which was primarily based on the biennial inspection frequency for domestic sites as previously established in section 510(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).
- The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 amended section 510(h) of the FD&C Act, replacing the fixed minimum inspection interval for domestic establishments (i.e., sites) with the requirement that FDA inspect domestic *and* foreign drug establishments "in accordance with a risk-based schedule" that considers establishments' "known safety risks." This defined a risk-based inspection frequency for all sites, regardless of location, to promote parity in inspectional coverage and the effective and efficient use of FDA resources to address the most significant public health risks. The statutory change

Originating Office: Office of Pharmaceutical Quality
Effective Date: 9/26/18 Page 1 of 7

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RISK BASED SITE SELECTION MODEL – MAPP 5014.1 (CONTINUED)

The following are currently identified as risk factors for inclusion in the SSM:

***Inherent product risk:**

- **Dosage form**
- **Route of administration**
- **Products intended to be sterile**
- **API load**
- **Biologic drug substance or drug product**
- **Therapeutic class**
- **Narrow Therapeutic Index (NTI) drugs**
- **Emergency use drugs**

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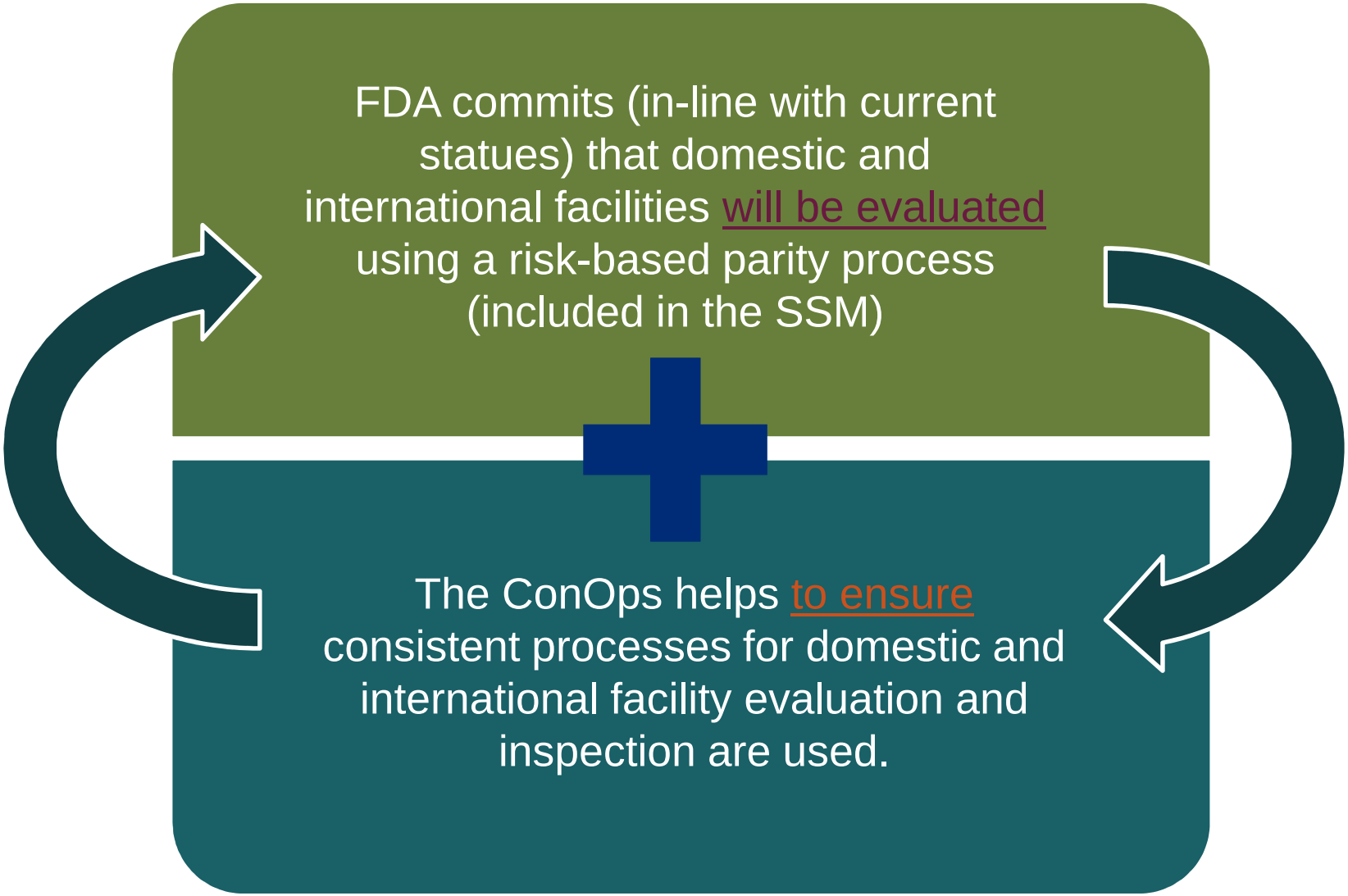
SITE SELECTION: FOREIGN VERSUS DOMESTIC



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PRE- APPROVAL INSPECTIONS (PAI / PLI*)

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PRE-APPROVAL INSPECTIONS

- **Pre-Approval Facility Evaluations and Inspections** directly support the assessment of marketing applications.

- **Pre-Approval *Facility Evaluations* are led by CDER with ORA participation.** This evaluation considers available information about each facility named in a marketing application, the drug being manufactured, and other information in the application to *determine 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*.** This type of inspection directly supports the assessment of marketing applications for drug product by evaluating the adequacy of the manufacturing processes and control strategy to ensure 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.*

**** Most CDER BLA Inspections are led by CDER (Office of Process & Facilities and/or Office of Biotechnology Products), and ORA may participate***

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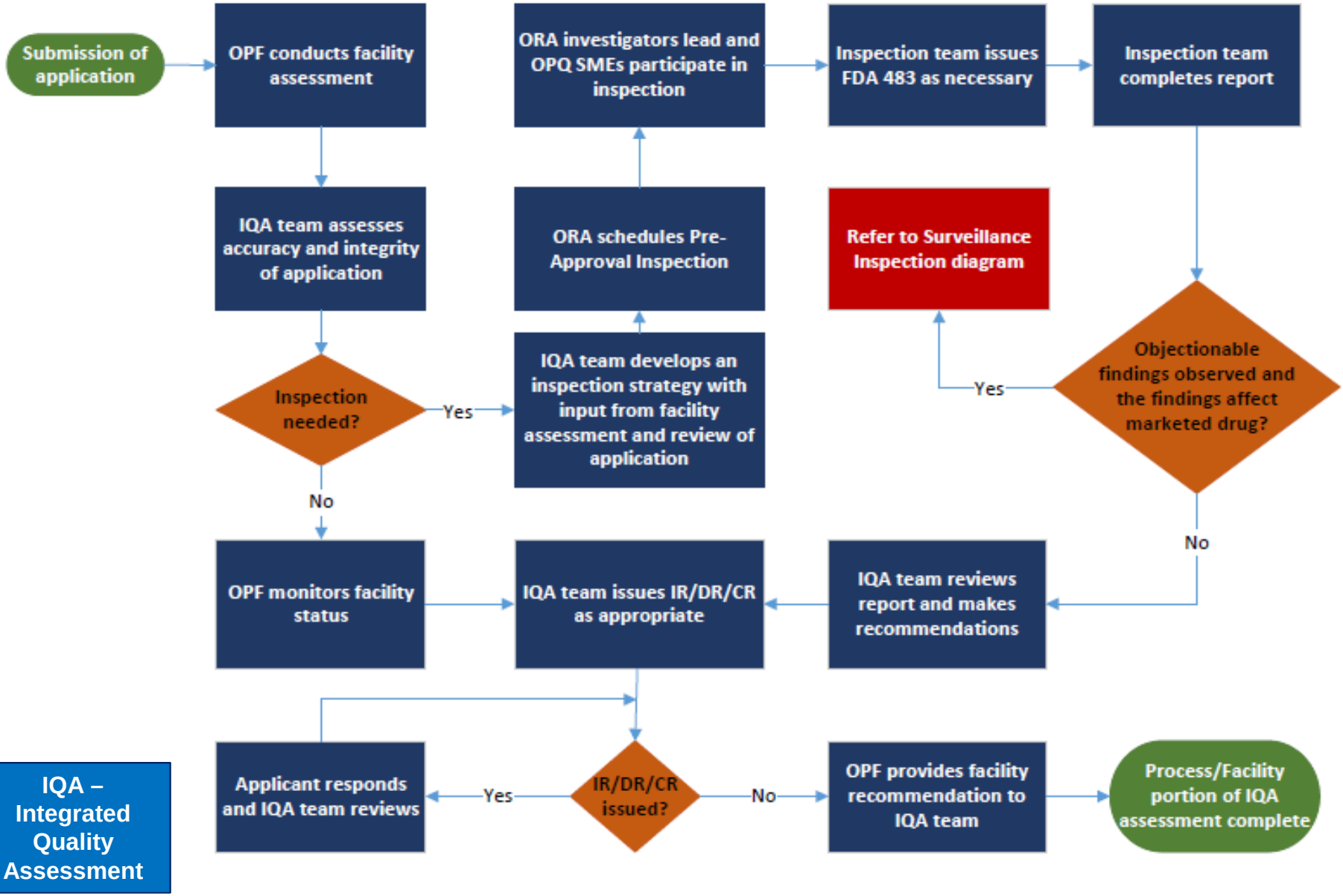
Pre-Approval Facility Inspection



IQA – Integrated Quality Assessment

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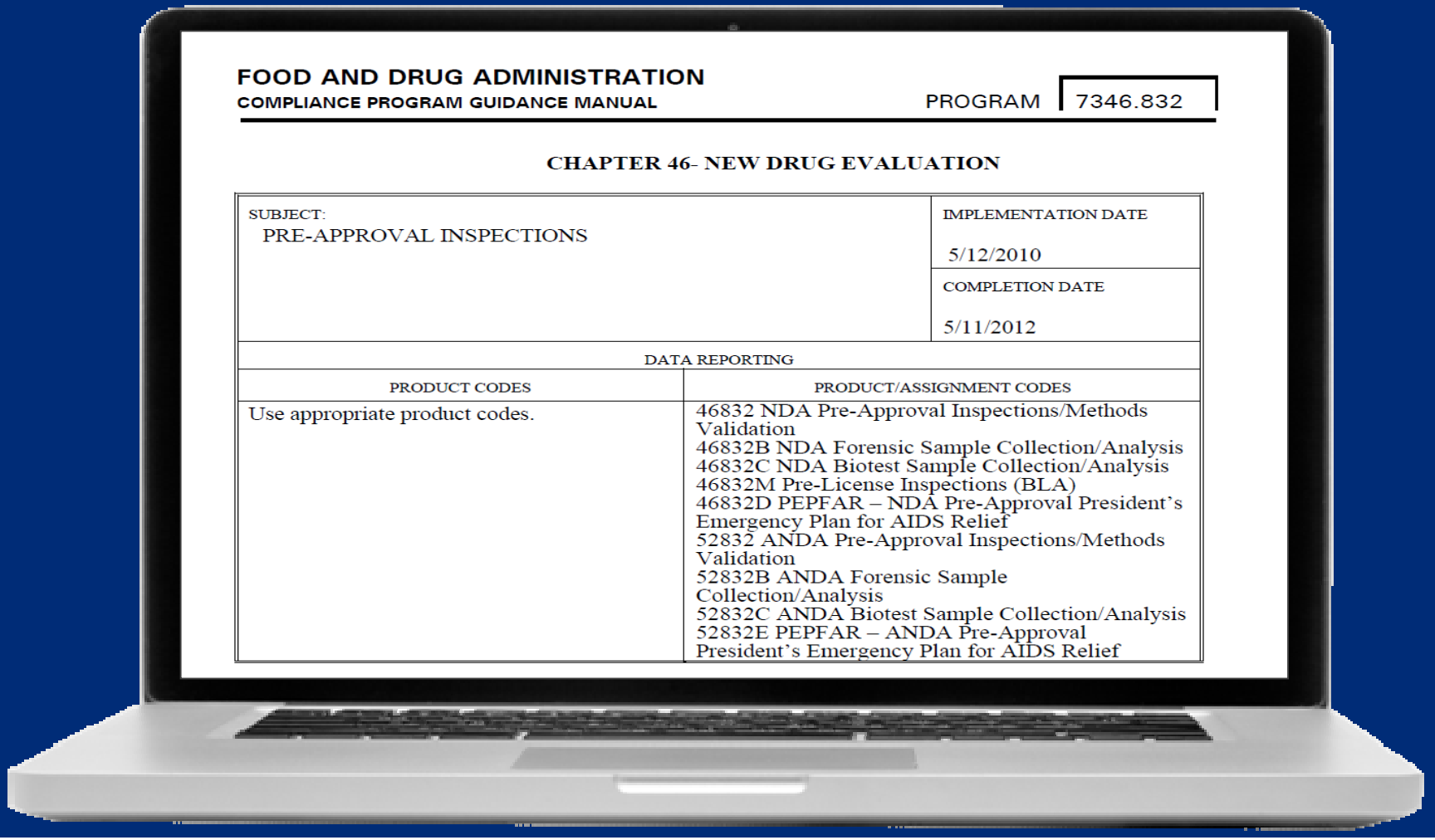
CPGM 7346.832 - UPDATE PENDING

http://wayback.archive-it.org/7993/20170112023320/http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf



FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL

PROGRAM 7346.832

CHAPTER 46- NEW DRUG EVALUATION

SUBJECT: PRE-APPROVAL INSPECTIONS	IMPLEMENTATION DATE 5/12/2010
	COMPLETION DATE 5/11/2012

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use appropriate product codes.	46832 NDA Pre-Approval Inspections/Methods Validation 46832B NDA Forensic Sample Collection/Analysis 46832C NDA Biotest Sample Collection/Analysis 46832M Pre-License Inspections (BLA) 46832D PEPFAR – NDA Pre-Approval President's Emergency Plan for AIDS Relief 52832 ANDA Pre-Approval Inspections/Methods Validation 52832B ANDA Forensic Sample Collection/Analysis 52832C ANDA Biotest Sample Collection/Analysis 52832E PEPFAR – ANDA Pre-Approval President's Emergency Plan for AIDS Relief

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PRE-APPROVAL INSPECTION OBJECTIVES (1)

Objective 1

Readiness for Commercial Manufacturing

- A ***quality system*** designed to achieve sufficient control over the facility and commercial manufacturing operations
- ***Manufacturing and laboratory changes, deviations, and trends*** relating to the development of new drug substance and product manufacturing have been adequately evaluated
- A sound and appropriate program for ***sampling, testing, and evaluation*** of components, in-process materials, finished products, containers and closures for the purpose of releasing materials or products has been established, including a robust ***supplier qualification program***
- The establishment has sufficient facility and equipment controls in place to ***prevent contamination***
- ***Adequate procedures*** exist for batch release, change control, investigating failures, deviations, complaints, and adverse events; and for reporting this information to FDA, such as field alert reporting
- The ***feasibility of the proposed commercial process*** and manufacturing batch record, including instructions, processing parameters and process control measures, are scientifically and objectively justified. ***This objective is linked to the firm's process validation program***

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PRE-APPROVAL INSPECTION OBJECTIVES (2 & 3)

Objective 2

Conformance to Application

- Verification that the formulation, manufacturing or processing methods, and analytical (or examination) methods are ***consistent with descriptions contained in the CMC section of the application*** for the bio batch (and other pivotal clinical batches, when applicable), the proposed commercial scale batch, and the API(s).

Objective 3

Data Integrity Audit

- Audit of the raw data, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, bio batch data) were submitted in the CMC section such that the CDER reviewer team can ***rely on the submitted data as complete and accurate***.

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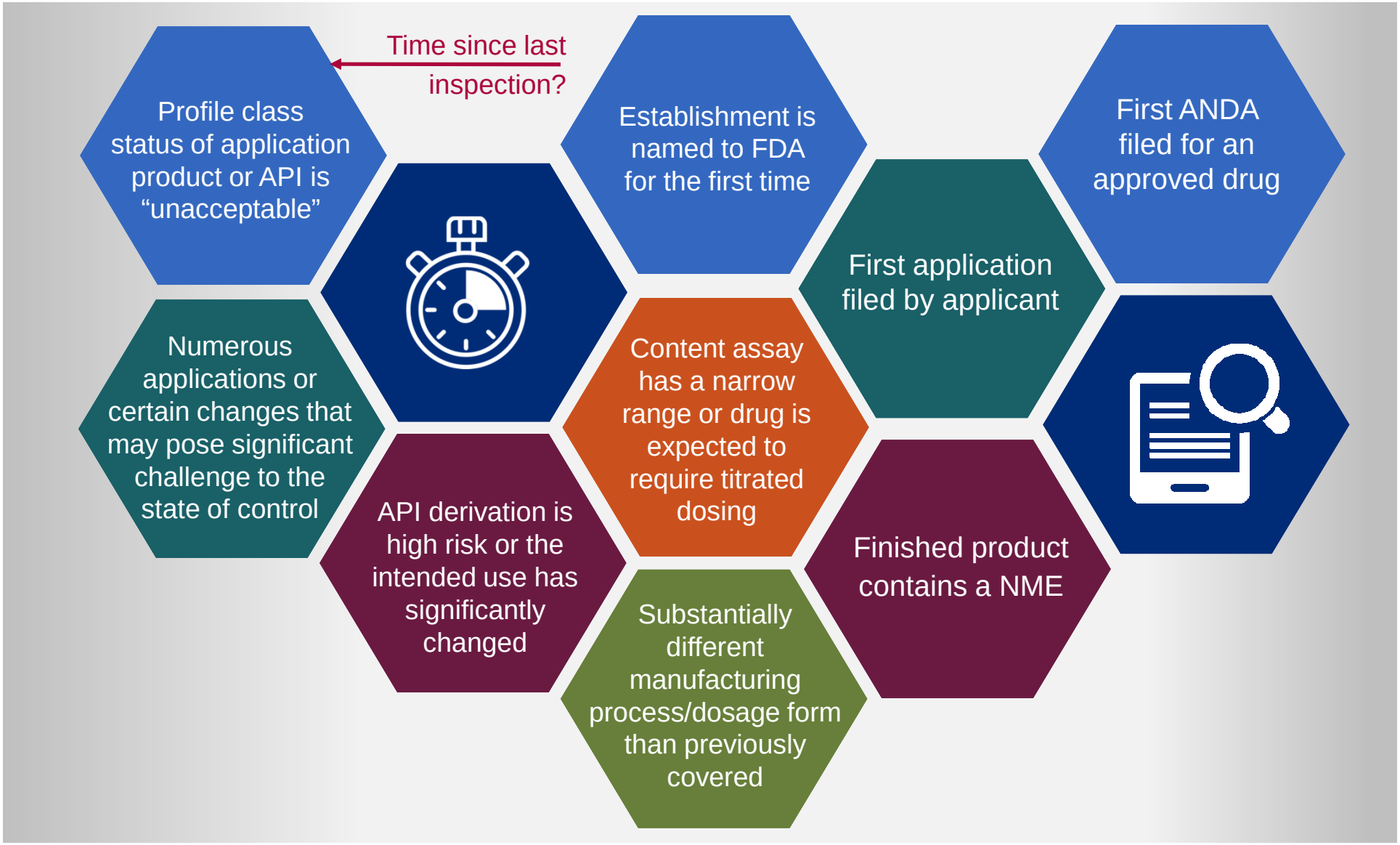
PRIORITY PRE-APPROVAL INSPECTION CRITERIA



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A LITTLE ON PROCESS VALIDATION (LINKED TO PAI OBJECTIVE #1)

2011 Guidance for Industry - Process Validation: General Principles and Practices

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

Process validation involves a series of activities taking place over the lifecycle of the product and process.

- Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

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POST- APPROVAL INSPECTIONS

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POST-APPROVAL INSPECTIONS

- **Post-Approval Facility Inspections are similar to PAIs as they are product specific, but are conducted after applications have been approved.**
- This type of inspection focuses largely on the *process validation lifecycle* and *any manufacturing changes* that may have occurred following approval (also follow-up on post-approval "commitments")
- *Changes in perceived risk may also initiate such an inspection*, even in cases where a Pre-Approval Inspection was not deemed necessary.
- **Post-Approval Facility Inspections are led by ORA with CDER participation.**
- This type of inspection ensures *commercial-scale processes* for an approved drug product conform to application commitments and CGMP requirements.
- The inspection information is used to *update lifecycle risks* for a specific drug product or to determine any regulatory actions.

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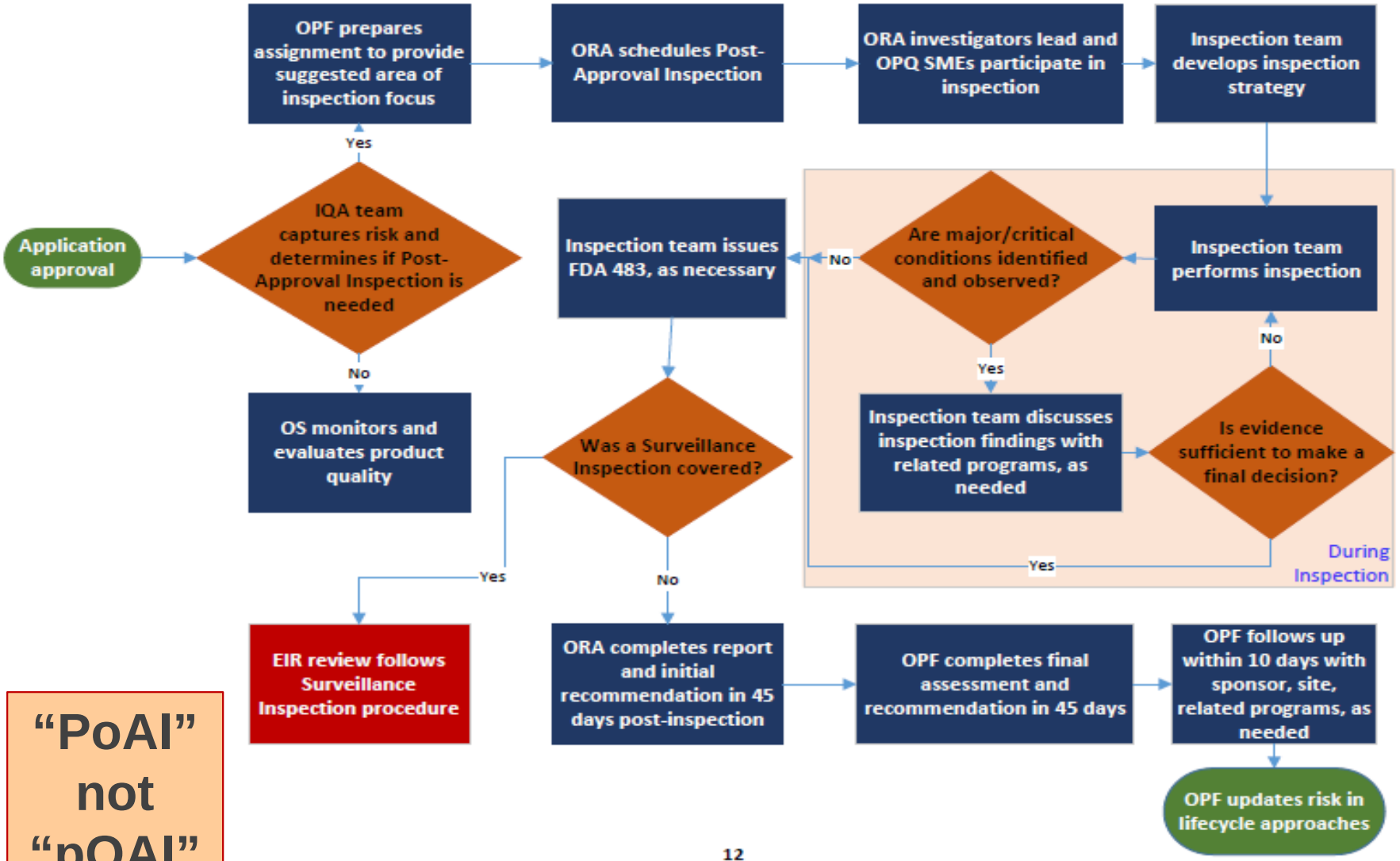
Post-Approval Facility Inspection



"PoAI" not "pOAI"

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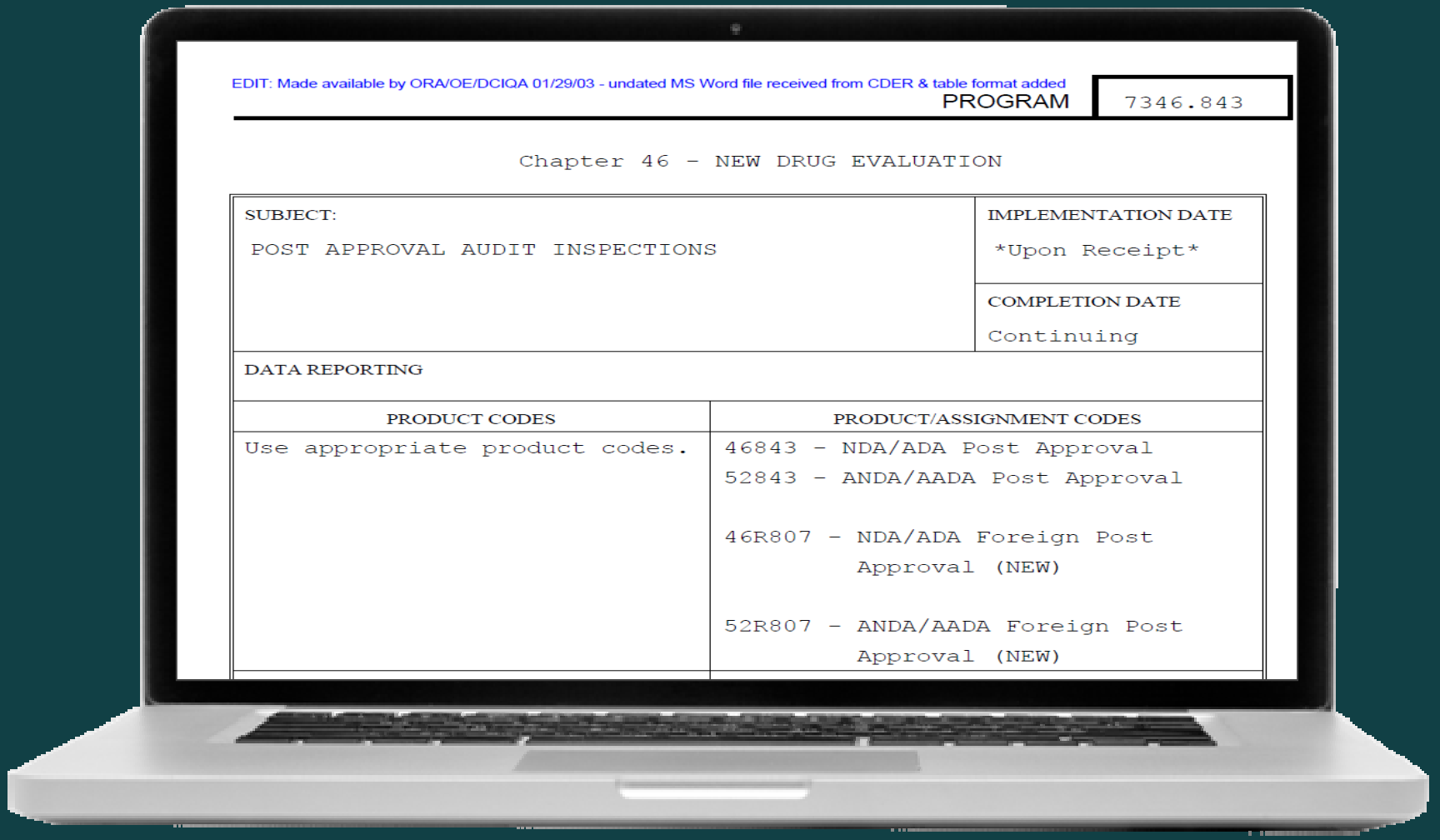
CPGM 7346.843 - UPDATE PENDING

https://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM125398.pdf



EDIT: Made available by ORA/OE/DCIQA 01/29/03 - undated MS Word file received from CDER & table format added

PROGRAM 7346.843

Chapter 46 - NEW DRUG EVALUATION

SUBJECT:	IMPLEMENTATION DATE
POST APPROVAL AUDIT INSPECTIONS	*Upon Receipt*
	COMPLETION DATE
	Continuing

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Use appropriate product codes.	46843 - NDA/ADA Post Approval 52843 - ANDA/AADA Post Approval 46R807 - NDA/ADA Foreign Post Approval (NEW) 52R807 - ANDA/AADA Foreign Post Approval (NEW)

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"FOR-CAUSE"

INSPECTIONS

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FOR-CAUSE INSPECTIONS

- **For-Cause Facility Inspections** are 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.
- This type of inspection is meant to gather additional information *to determine the quality of marketed product and to determine whether enforcement actions are warranted*.
- These 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 Facility Inspections with CDER participation, when appropriate.**
- ORA investigators carry out For-Cause Inspections on facilities identified by ORA, CDER or other sources.
- For-Cause Inspections can focus on specific issues and evaluate a firm's conformance to CGMPs.

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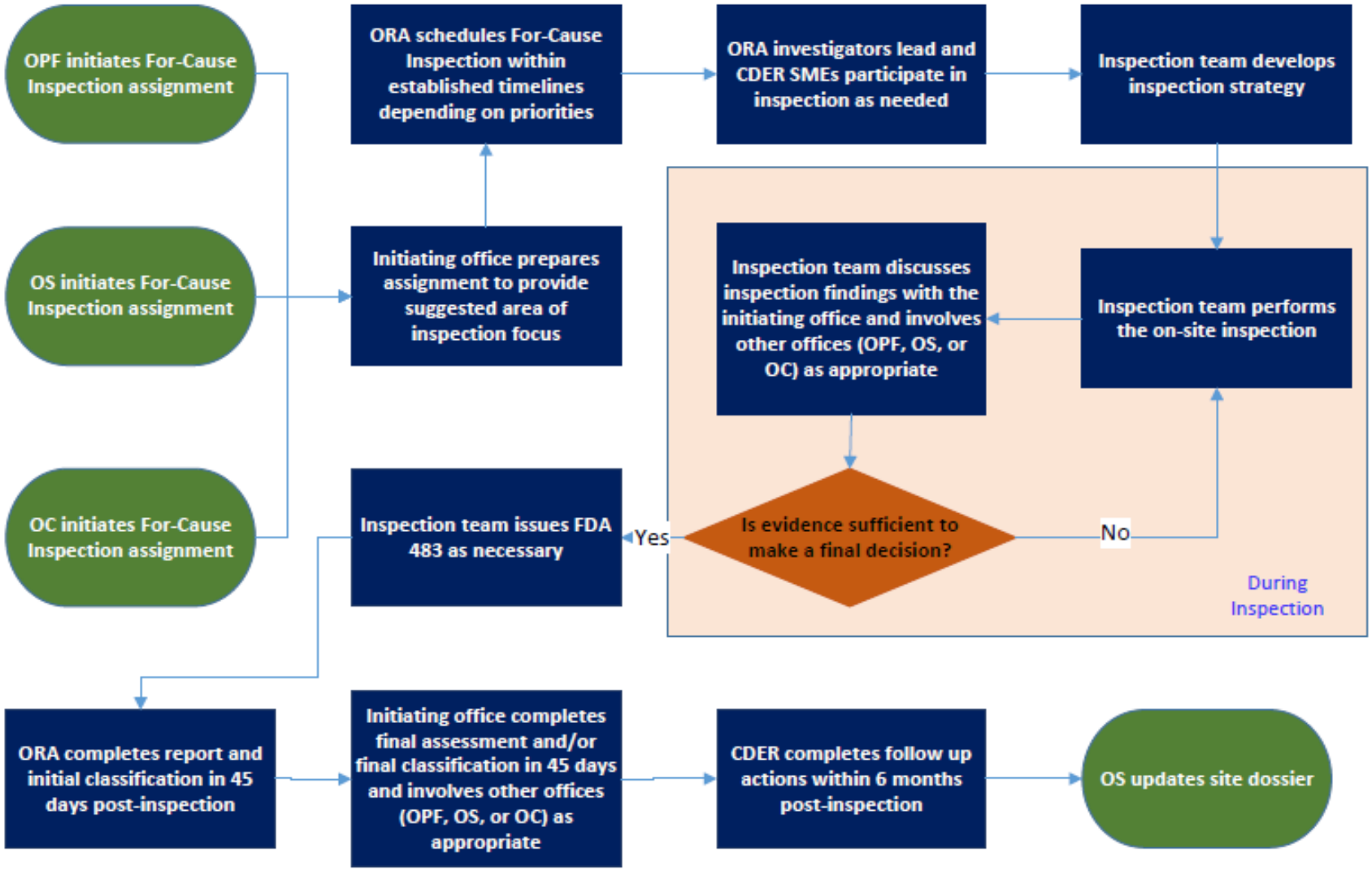
For-Cause Facility Inspection



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INSPECTION DATABASE

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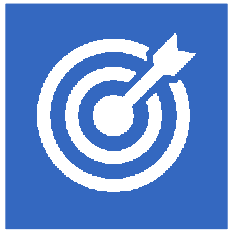
INSPECTION DATABASE (1)

Https://www.fda.gov/ICECI/Inspections/ucm222557.htm



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

For a firm's current compliance status, it is important to check the Inspection Classification Database for updates.

To learn more about the Inspection Classification Database, visit the FAQs page.

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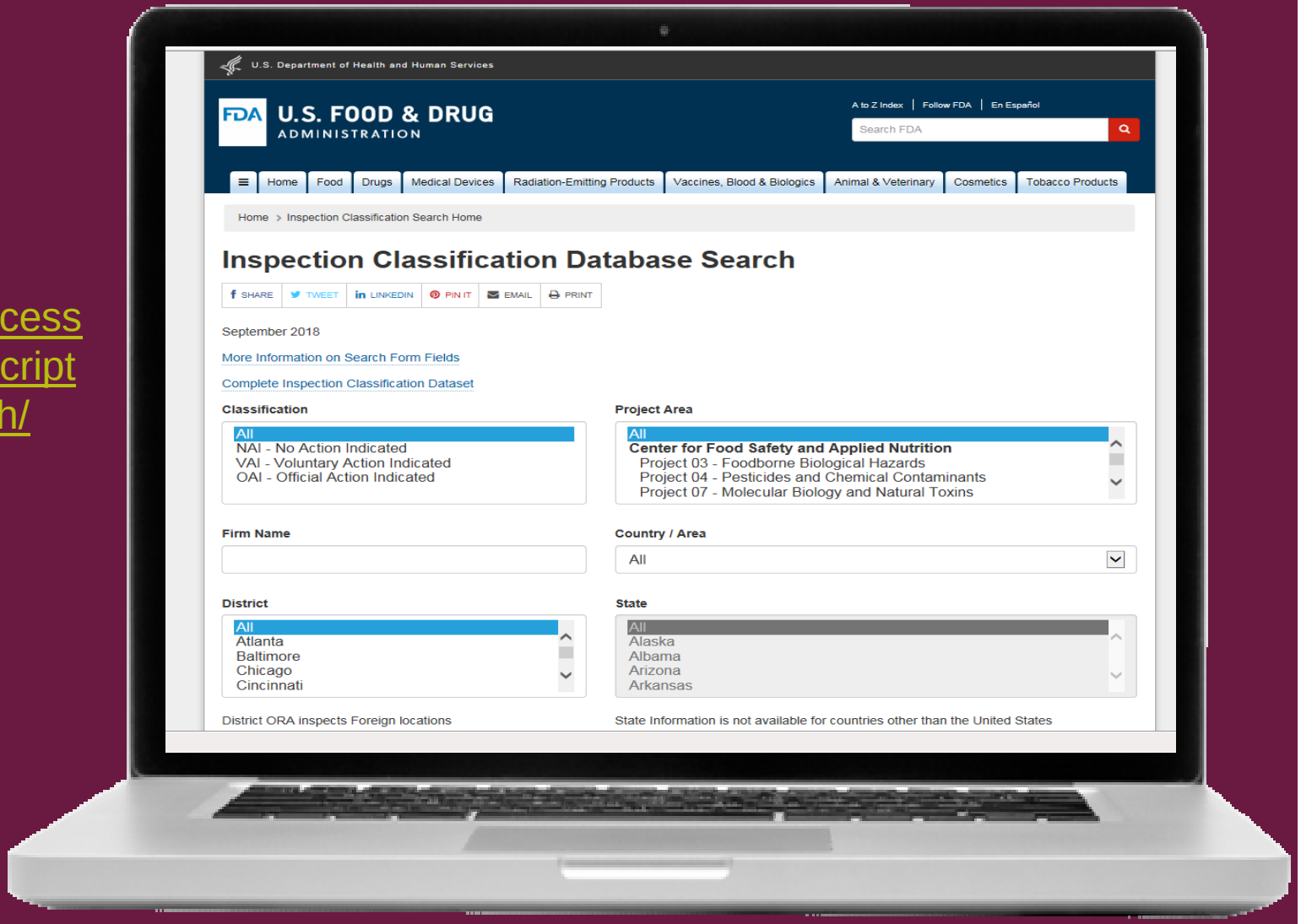
INSPECTION DATABASE (2)

https://www.accessdata.fda.gov/scripts/inspsearch/



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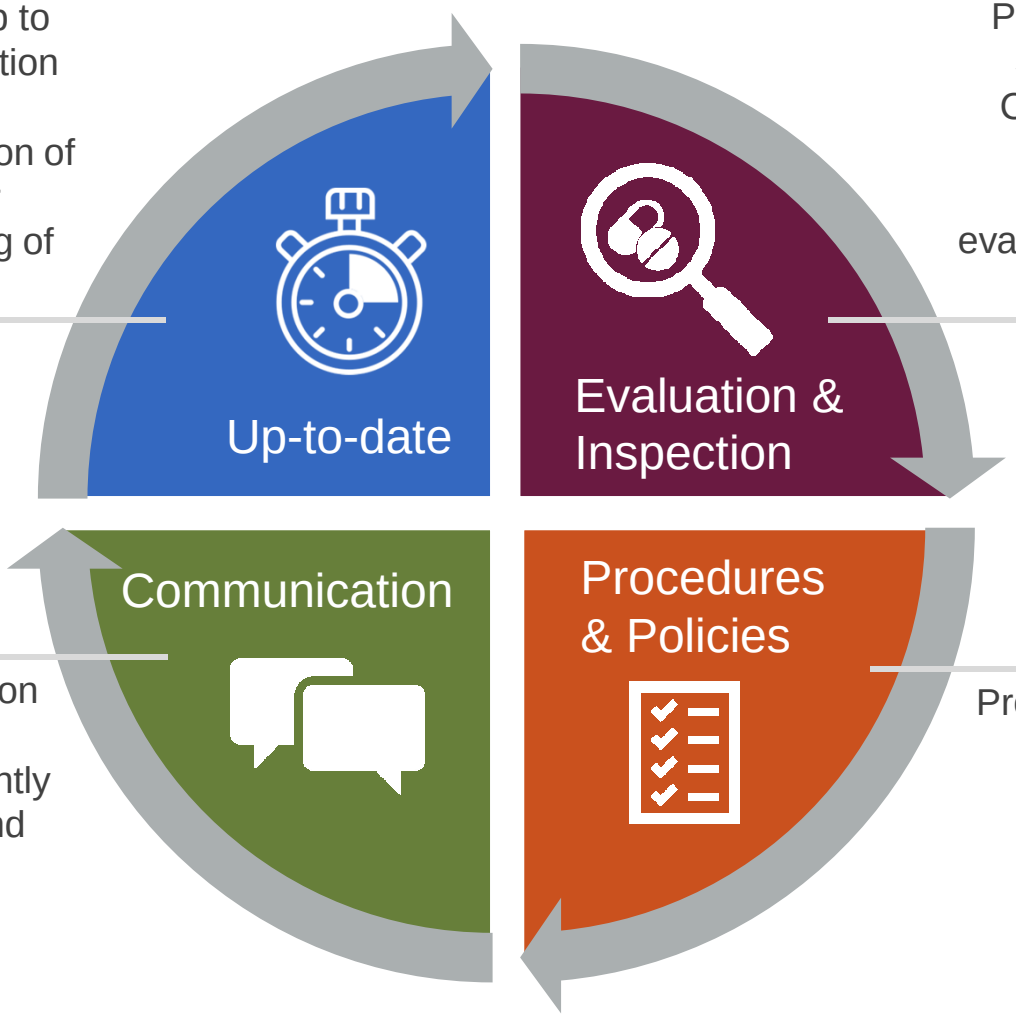
SUMMARY

It is important to stay up to date on current information and policies related to evaluation and inspection of facilities responsible for manufacture and testing of human drugs

The ConOps applies to Pre-and Post-Approval, Surveillance, and For-Cause Inspections and "outlines an operating model for facility evaluation and inspection for human drugs



Increased communication and transparency are evident based on currently available documents and web resources

Procedures and policies for each type of inspection are being revised under the ConOps

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ABOUT PAREXEL

- A leading global biopharmaceutical services organization
- 30+ years assisting clients in pharmaceutical, biotechnology, and medical device industries
- We are physicians, technologists, business process experts, and more

WE ARE A TEAM OF EXPERTS DEDICATED TO YOUR JOURNEY TO MARKET.

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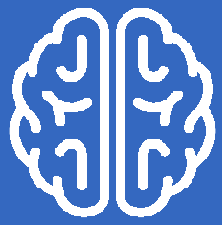
WHAT WE OFFER

PAREXEL is focused on end-to-end integrated solutions – from product strategy and clinical development through market access and lifecycle management.

We simplify the journey between science and new treatments by applying:



BEST MINDS

INNOVATION

PROBLEM-SOLVING

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THANK YOU

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QUESTIONS

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https://regulatory.parexel.com/

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