Concept of Operations

--How It May Impact Inspections, Review and Approval

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IPA Annual Conference:

Towards Excellence in Quality

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Agenda:

1. What is the Concept of Operations (ConOps)?
2. What is the scope of ConOps?
3. How ConOps may impact inspections, Review, and Approval?
   - Pre-Approval Inspections (PAI)
   - Post-Approval Inspections
   - Surveillance Inspections
   - For-Cause Inspections
   - Import alerts and others
4. Questions

Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations

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On June 6, 2017, the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) have entered into an unprecedented concept of operations (ConOps) agreement to integrate facility evaluations and inspections for human drugs. The agreement, Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations, outlines the responsibilities and the workflow for Pre-Approval, Post-Approval, Surveillance, and For-Cause Inspections at domestic and international facilities.
ConOps will enable CDER and ORA to more effectively manage the growing complexity of the pharmaceutical landscape and to meet new challenges by:

Reference Link for the FDA ConOps white paper:

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/UCM574362.pdf

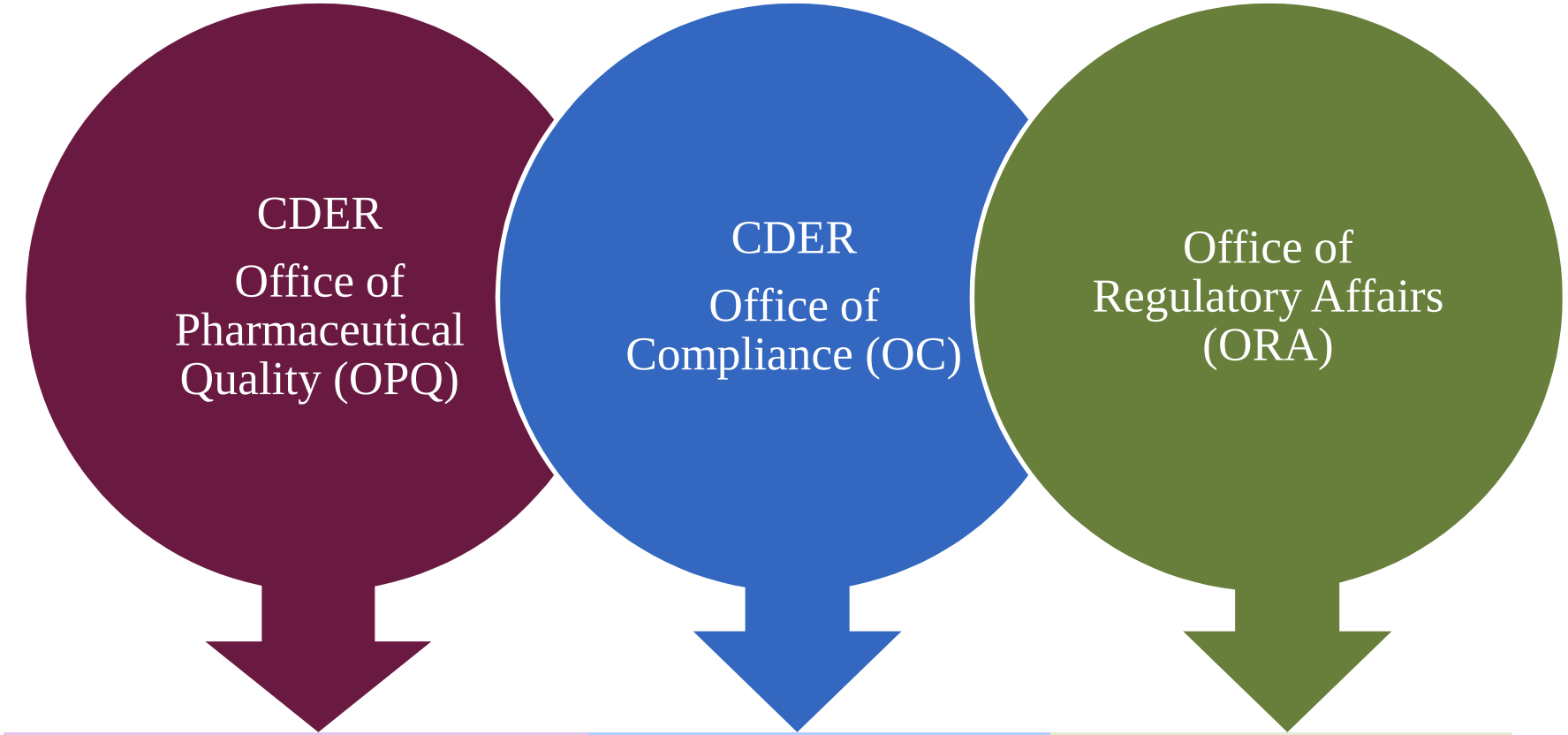
Note: Information in some of the slides are from the US FDA website and associated documents.

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.

- Enables CDER and ORA to more effectively manage the growing complexity of the pharmaceutical manufacturing and to meet new challenges.

Key FDA Groups Included in the ConOps:



ConOps

Complementary to the Program Alignment initiative in ORA

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

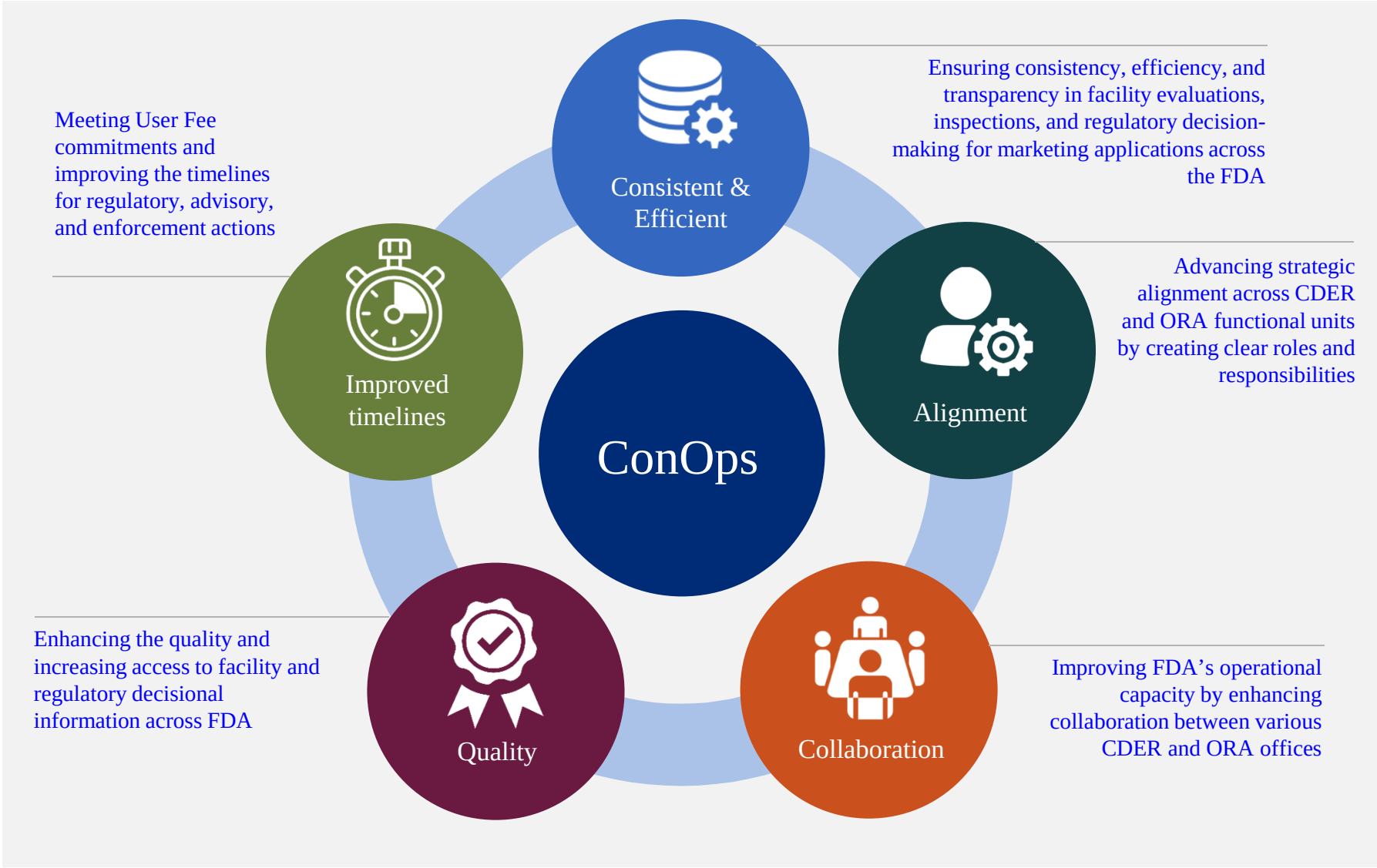
Why ConOps and How?

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.

Why ConOps and How?



The Impact of ConOps: xxUFA (PDUFA, GDUFA, BsUFA….)

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) or other user fee programs timeframes for Pre-Approval Inspections

CDER and ORA is issuing the 90-day decisional letters with a goal of 90 percent

The Scope of ConOps:

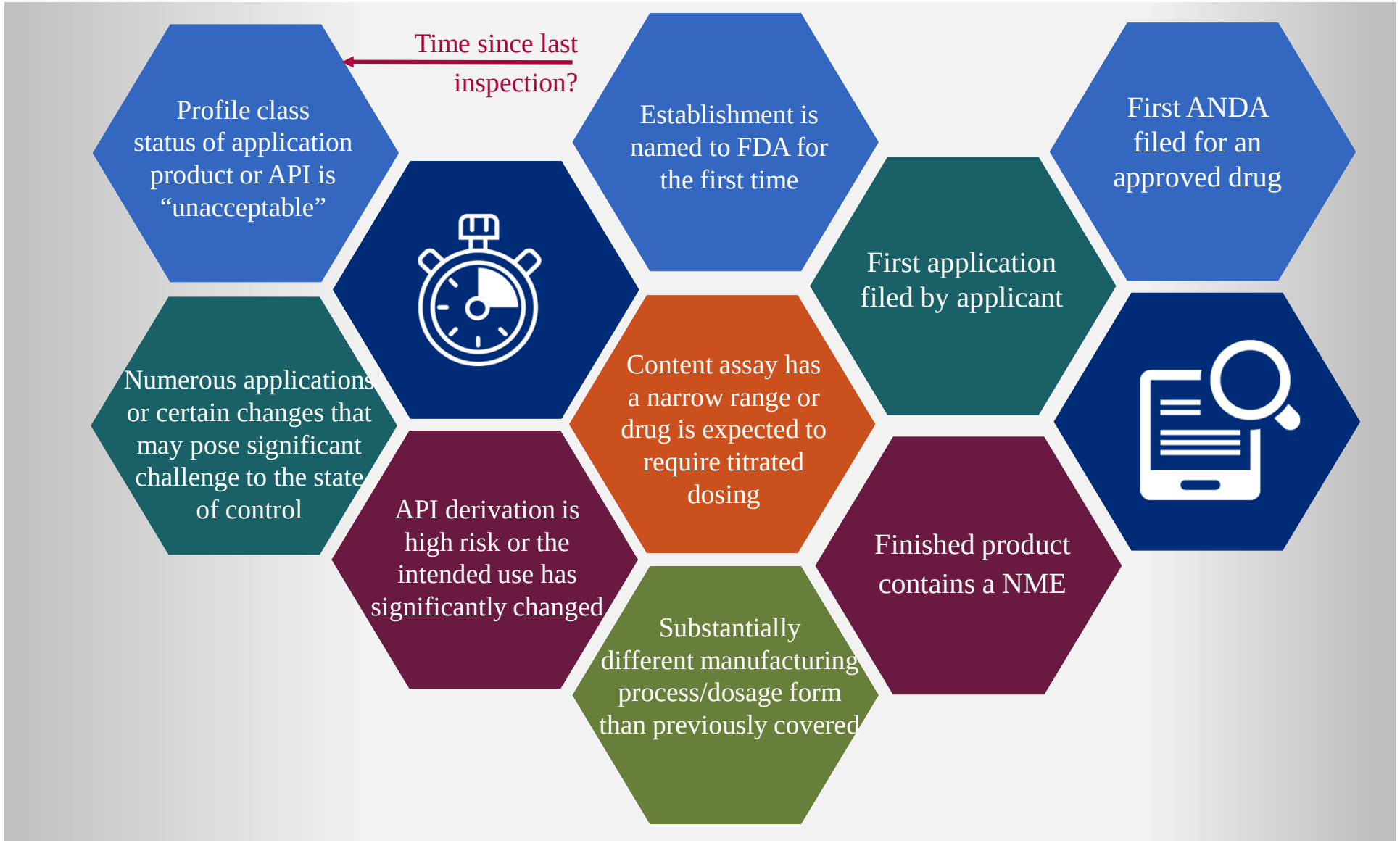
Applies to:

- **Pre-Approval (PAI)**
- **Post-Approval**
- **Surveillance**
- **For-Cause Inspections**

Type of Inspection	Leading Center	Purpose	Outcome	Sponsors
Pre-approval	CDER	Approvability (quality)	IR, DRL, or CRL	**To address all questions listed in the letter asap**
	ORA	Approvability (overall)	IR, DRL, or CRL	
Type of Inspection	**Leading Center**	**Purpose**	**Outcome**	**Sponsors**
Post-approval	ORA	cGMP compliance	483s	**To address all citations asap**

IR: Information Request
DRL: Discipline Review Letter
CRL: Complete Response Letter

Priority Pre-Approval Inspection Selection Criteria:



Scenario 1: Pre-Approval Facility Evaluations are led by CDER with ORA participation:

- Using information provided in the application to determine if Pre-Approval Inspection is needed
- To support decision-making regarding the approvability of a marketing application from **a quality** perspective.

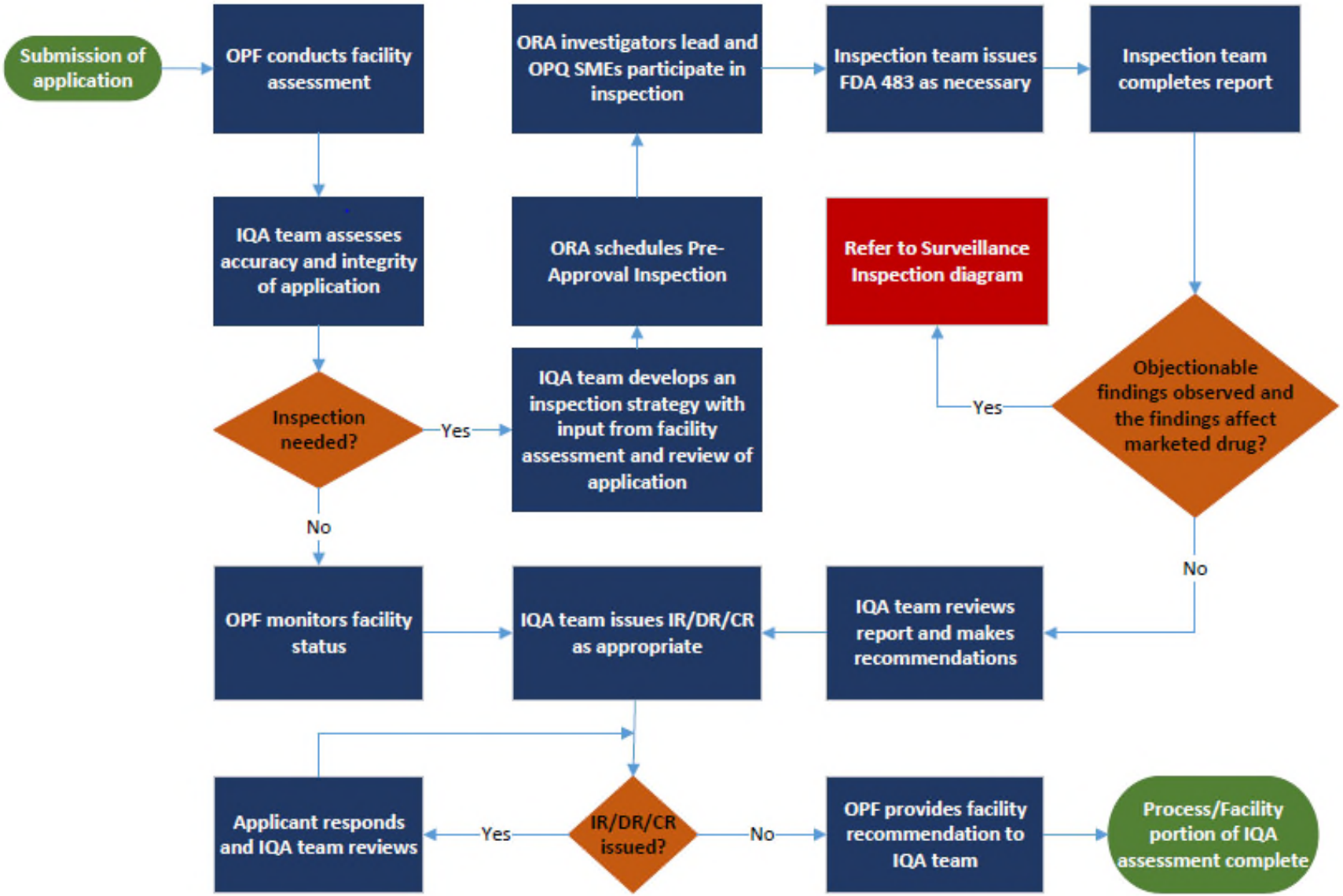
- **Sponsor: if needed, contact the OPQ review team through RBPM for any questions.**

Scenario 2: Pre-Approval Inspections are led by ORA with CDER participation:

- To support the assessment of marketing applications for drug products 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.

- **Sponsor: if needed, contact the review team through RPM (OND or OGD) for any questions.**

Pre-Approval Facility Inspection



RACI Chart for PAI: accountability is clear and no overlap!

R: Responsibility; A: Accountability; C: Consulted; I: Informed

Tasks	OPQ/ OPF	OPQ (IQA)	ORA/ Pharm	CDER	ORA
Conduct facility evaluation	R	C	I	A	
Assess accuracy and integrity of the application	C	R	I	A	
Select facility for inspection	R	C	C	A	
Develop inspection strategy	C	R	C	A	
Schedule inspection	I	I	R		A
Conduct inspection	C	C	R		A
Issue FDA 483 as necessary	C	C	R		A
Complete inspection report	C	C	R		A
Review the inspection report and make recommendations	C	R	C	A	
Monitor facility status	R	I	I	A	
Issue IR/CR as appropriate	C	R	C	A	
Provide facility recommendation	R	I	I	A	

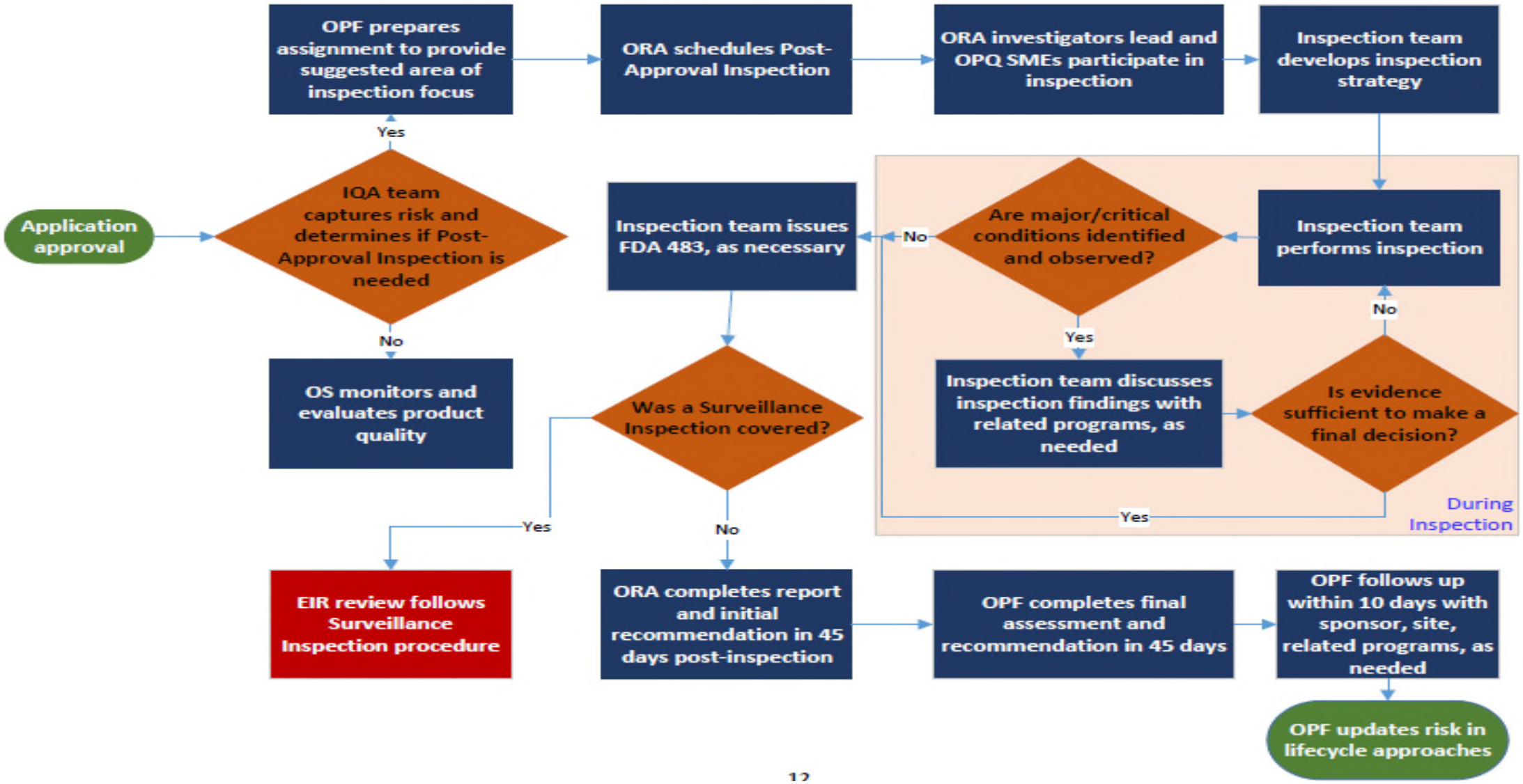
Post-Approval: conducted after applications have been approved. This type of inspection focuses largely on:

- Process validation
- Lifecycle
- Manufacturing changes (occurred post approval)

Post-Approval Facility Inspections are led by ORA with CDER participation: To ensures commercial-scale processes for an approved drug product conform to application commitments and cGMP requirements.

Sponsor: if any 483s issued, make sure the response is sent back on time and corrective actions are taken within the committed time frame. If there is any questions regarding the inspection, contact the ORA regional office or CDER offices (OND, OGD, or OPQ) depend on the nature of the question.

Post-Approval Facility Inspection



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RACI Chart for Post Approval Inspections: accountability is clear and no overlap!

R: Responsibility; A: Accountability; C: Consulted; I: Informed

Tasks	OPQ/ OPF	ORA/ Pharm	CDER	ORA
Identify high risk products / facilities for post-approval coverage	R	I	A	
Prepare assignment	R	C	A	
Schedule Post-Approval Inspection	C	R		A
Form inspection team	C	R		A
Develop inspection strategy	C	R		A
Perform inspection	C	R		A
Discuss inspection findings	C	R		A
Issue FDA 483, as needed	C	R		A
Complete report and initial recommendation in 45 days post-inspection	I	R		A
Complete final recommendation in 45 days	R	C	A	
Complete follow up actions in 10 days	R	C	A	

Surveillance Facility Inspections: focus on facilities that manufacture marketed:

- Prescription drugs
- Over-the-counter monograph drug products
- In-process materials or drug substances used in marketed drug products.

To monitor the conformance to CGMP requirements and is not necessarily an assessment of a specific product. Rather, it is a **system-based inspection**. 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.

ORA leads Surveillance Facility Inspections with CDER participation, when requested by ORA. ORA investigators carry out Surveillance Inspections at facilities identified by **CDER's surveillance risk model**.

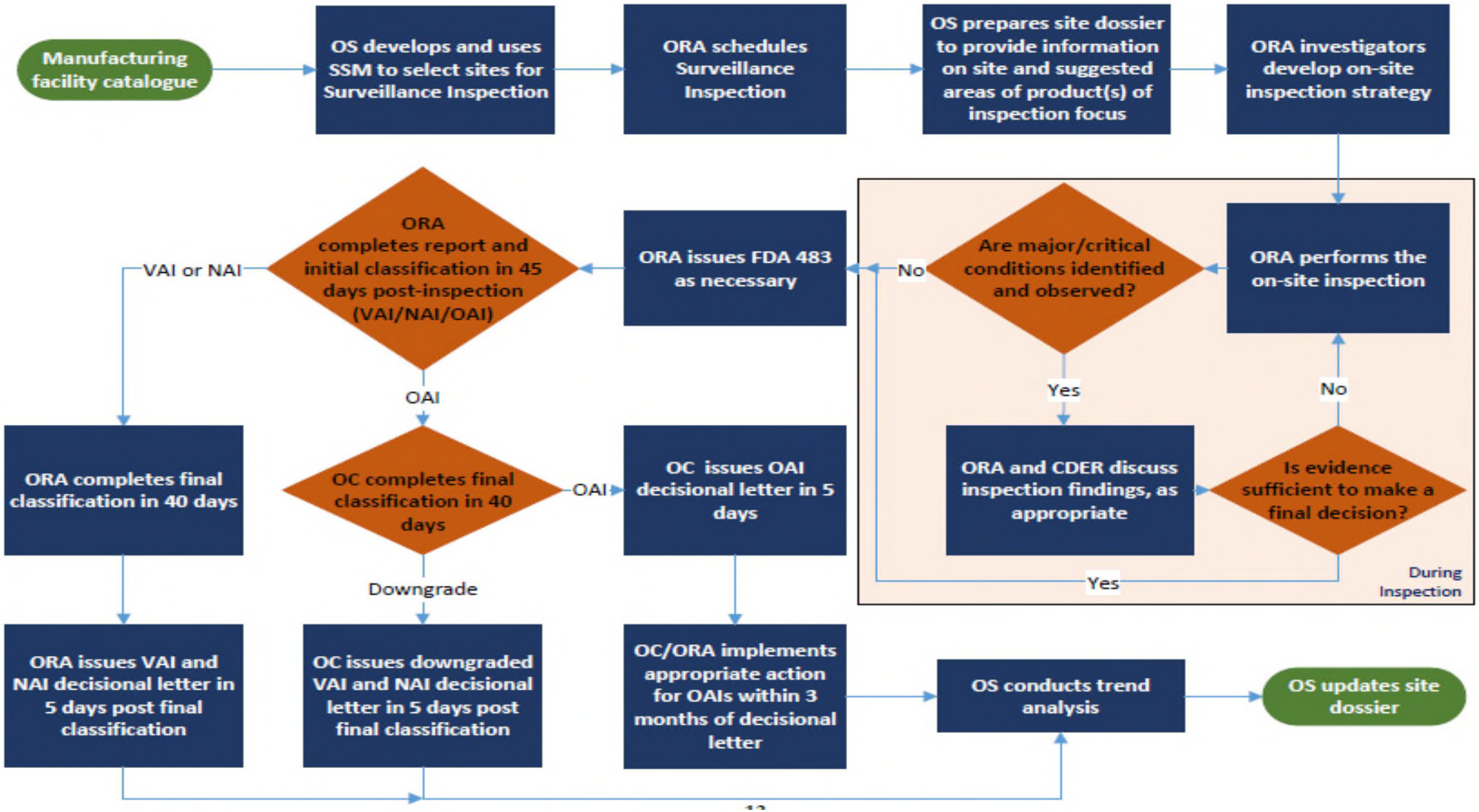
Message:

If form 483 is issued, make the correction as soon as you can, if there are any clarifications or questions regarding the citation, contact the relevant FDA office/center as soon as you can to ensure you are on the right path to be removed from OAI alert list if applicable, thus your application can be cleared in a timely manner.

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.**

Surveillance Facility Inspection



RACI Chart for Surveillance Inspections: accountability is clear and no overlap!

R: Responsibility; A: Accountability; C: Consulted; I: Informed

Tasks	OPQ/ OS	ORA/ Pharm	OC/ OMQ	CDER	ORA
Maintain manufacturing facility catalogue	R	C	I	A	
Develop Site Selection Model	R	C	I	A	
Select sites for Surveillance Inspection	R	C	I	A	
Schedule inspection	I	R	I		A
Prepare site dossier	R	C	I	A	
Develop on-site inspection strategy	C	R	I		A
Perform inspection	I	R	I		A
Convene discussion, as appropriate, if major/critical conditions identified	C	R	C		A
Issue FDA 483 as necessary	I	R	I		A
Complete report and initial classification in 45 days post-inspection	I	R	I		A
Complete final classification for NAIs and VAIs in 40 days	I	R	I		A
Issue NAI and VAI decisional letter in 5 days post final classification	I	R	I		A
Complete final classification for OAIs and issue OAI decisional letter	C	C	R	A	
If OAI downgraded, issue VAI or NAI decisional letter in 5 days post final classification	I	I	R	A	
Implement appropriate action for OAIs within 3 months of decisional letter	C	C	R	A	
Conduct trend analysis	R	I	I	A	
Update site dossier	R	I	I	A	

For-Cause Facility Inspections:

- New registrant
- A specific event or information that brings into question the compliance and/or quality of a manufacturing practice, facility, process, or drug.
- To gather additional information to determine the quality of marketed product
- 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.

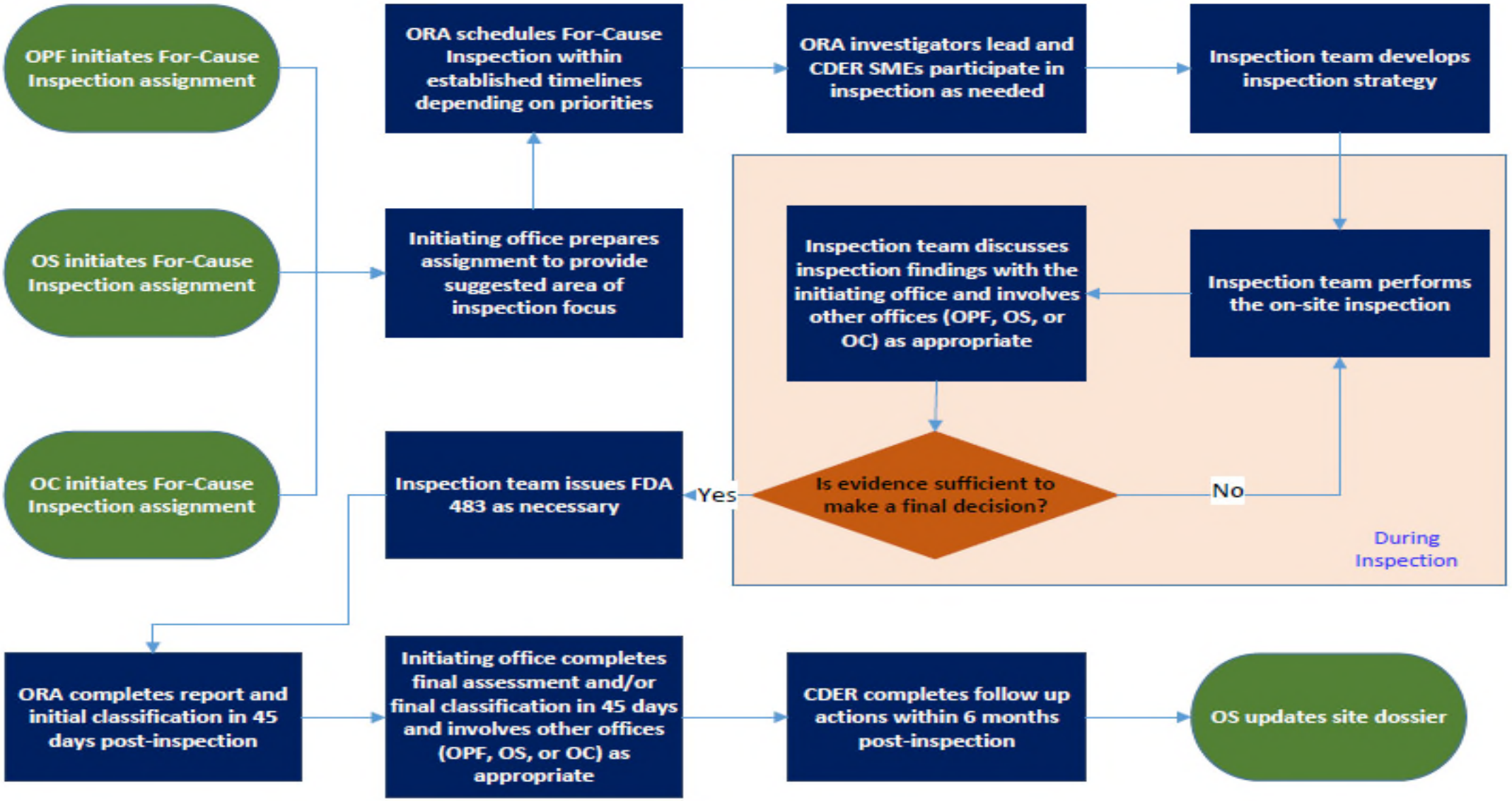
For-Cause Facility Inspections:

- 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.**

Message:

Know the "cause" (why the inspector is at the door) and if 483 is received, make the correction as soon as you can, if there are any clarifications or questions regarding the citation, contact the relevant FDA office/center as soon as you can to ensure you are on the right path to be removed from the alert list, thus your application can be cleared in the timely manner.

For-Cause Facility Inspection



RACI Chart for For-Cause Inspections: accountability is clear and no overlap!

R: Responsibility; A: Accountability; C: Consulted; I: Informed

Tasks	CDER (OC, OS, or OPF)	ORA/ Pharm	CDER	ORA
Initiate For-Cause Inspection assignment	R	I	A	
Prepare assignment	R	C	A	
Schedule For-Cause Inspection	C	R		A
Form inspection team	C	R		A
Develop inspection strategy	C	R		A
Perform inspection	C	R		A
Discuss inspection findings	C	R		A
Issue FDA 483 as needed	C	R		A
Complete initial classification and inspection report in 45 days post-inspection	I	R		A
Complete final assessment and/or final classification in 45 days	R	C	A	
Complete follow up actions within 6 months post-inspection	R*	C	A	

* If a major issue is identified, responsibility may be transferred to the other CDER offices; if no major issue is identified, responsibility remains with initiating office

How Does FDA Communicate the Final Inspection Classification?

- The ConOps created 90-day facility classification decisional letters **"90-day decisional letter"**
- 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):** for firms outside of USA, IA 66-40, Import Alert for GMP violations, will be issued. And any pending applications (NDA, ANDA, BLA etc) can't be approved.

90-day decisional letter

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

Import Alert (IA 66-40): an issue for facility that is under OAI

- 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.

Import Alert (IA 66-40):

Number of Import Alerts by Country/Area

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Country/Area
AFGHANISTAN
ALBANIA
ALGERIA
ANDORRA
ANTIGUA & BARBUDA
ARGENTINA
ARMENIA
ARUBA

Import Alert 66-40

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(Note: This import alert represents the Agency's current guidance to FDA field personnel regarding the manufacturer(s) and/or products(s) at issue. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public).

Import Alert # 66-40
Published Date: 02/14/2019
Type: DWPE

Import Alert Name:

"Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs"

Reason for Alert:

*** Foreign inspections of pharmaceutical manufacturers are being performed. Detention without physical examination may be appropriate when an FDA inspection has revealed that a firm is not operating in conformity with current good manufacturing practices (GMP's).

55-05	DWPE	03/27/2018	DETENTION WITHOUT PHYSICAL EXAMINATION OF FINISHED DOSAGE DRUG PRODUCTS, ACTIVE PHARMACEUTICAL INGREDIENTS AND INACTIVE INGREDIENTS FOR POTENTIALLY HAZARDOUS MICROBIOLOGICAL CONTAMINATION
66-40	DWPE	02/14/2019	"Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs"
66-41	DWPE	01/08/2019	Detention Without Physical Examination of Unapproved New Drugs Promoted In The U.S.
66-57	DWPE	01/25/2018	"Detention Without Physical Examination Of Foreign manufactured Unapproved Prescription Drugs Promoted to Individuals in the U.S."

Import Alert (IA 66-40):

Delta Laboratories Pty Ltd — **Date Published : 09/28/2017**

8 Warringah CL , Somersby, New South Wales AUSTRALIA

55 - - - -- Pharm Necess & Ctnr For Drug/Bio	Date Published: 09/28/2017
Notes: All Drugs; Problem(s): (GMP) Good Manufacturing Practices	
56 - - - -- Antibiotics (Human/Animal)	Date Published: 09/28/2017
Notes: All Antibiotics; Problem(s): (GMP) Good Manufacturing Practices	
60 - - - -- Human and Animal Drugs	Date Published: 09/28/2017
Notes: All Drugs; Problem(s): (GMP) Good Manufacturing Practices	
61 - - - -- Human and Animal Drugs	Date Published: 09/28/2017
Notes: All Drugs; Problem(s): (GMP) Good Manufacturing Practices	
62 - - - -- Human and Animal Drugs	Date Published: 09/28/2017
Notes: All Drugs; Problem(s): (GMP) Good Manufacturing Practices	
63 - - - -- Human and Animal Drugs	Date Published: 09/28/2017
Notes: All Drugs; Problem(s): (GMP) Good Manufacturing Practices	
64 - - - -- Human and Animal Drugs	Date Published: 09/28/2017
Notes: All Drugs; Problem(s): (GMP) Good Manufacturing Practices	
65 - - - -- Human and Animal Drugs	Date Published: 09/28/2017
Notes: All Drugs; Problem(s): (GMP) Good Manufacturing Practices	
66 - - - -- Human and Animal Drugs	Date Published: 09/28/2017
Notes: All Drugs; Problem(s): (GMP) Good Manufacturing Practices	

These codes covers all drug categories

Import Alert (IA 66-40): an issue for facility that is under OAI

- **Get** your facility down graded to VAI as soon as possible, sometimes re-inspection is a must before this down grade can occur.
- **Communicate** with OMQ (Office of Manufacturing Quality, OC, CDER) regularly until the issue is resolved.
- **Correct** all findings from the previous inspection and inform the FDA (OMQ and district office of ORA) in writing that you are ready for re-inspection, YOU HAVE TO BE REALLY READY!
- **Start** the on-line petition process requesting for removal of your firm from the IA 66-40 list once the reinspection results are favorable.

Key: communication, communication and communication with FDA!

ConOps Impacts the Review and Approval of the Applications:

- Using ConOps model to streamline the facility inspection process and incorporate the **review** team assessment results into the decision making process.

- **Team based review** to ensure the review process is not siloed and ensure all UFA obligations are met. New ways to perform primary and secondary reviews have been explored and aiming at efficiency enhancing and patient centric/clinical relevance.

- The Warning Letter (WL) and enforcement action issuing process is going through process improvement and is the main focus of Office of Compliance new strategic goals.

Inspection Results Impact on Review and Approval:

- **Official Action Indicated (OAI):**
  - Review will not be a priority anymore even it was before the OAI, for CRL (complete response letter) can be issued when facility is OAI, and UFA goal date is met (a very important metric that FDA is tracking).
  - The risk associated with your application will be high under the risk model and risk based review practice.
  - More scrutinizing will be put into the review process, remember, it is a team based review for NDA and ANDA, all team members would be informed regarding your facility status.
  - No applications that associated with that facility can be approved until the OAI is downgraded.

Final thoughts:

- Facility is tightly linked to your applications or drug master file (for API manufactures).
- The ConOps implementation has linked the **inspection--review activities--approvability of an application** together and the previous siloed operation has changed.
- Timely communication with the appropriate office within the FDA is the key should your facility have any compliance/application issues.
- Always keep your facility in compliance with all current regulations, not only for inspection or approvability of your applications but for **the benefit of the patients who will take your medicine to save their lives and the trust they put in your products!**

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.

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

THANK YOU

Questions?

For more information:

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https://regulatory.parexel.com/