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

CENTER FOR DRUG EVALUATION AND RESEARCH
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1. INTRODUCTION

This concept of operations (ConOps) white paper will discuss 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. This ConOps applies to Pre- and Post-Approval, Surveillance, and For-Cause Inspections. This document outlines an operating model for facility evaluation and inspection for human drugs[1].

This envisioned operating model will enable FDA to better handle the growing complexity of the pharmaceutical landscape and to meet new challenges by[2]:

- Ensuring consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision-making for marketing applications across the FDA;
- Advancing strategic alignment across CDER and ORA functional units by creating clear roles and responsibilities;
- Improving FDA's operational capacity by enhancing collaboration between various CDER and ORA offices;
- Enhancing the quality and increasing access to facility and regulatory decisional information across FDA; and
- Meeting User Fee commitments and improving the timelines for regulatory, advisory, and enforcement actions to protect public health and promote drug quality, safety, and effectiveness.

The following offices played a significant role in the development of this ConOps:

- Center for Drug Evaluation and Research
  - 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

[1] Other than Compounding and Bioresearch Monitoring

[2] This concept of operations will also serve as a foundational component as the pharmaceutical program develops new tools and techniques for assessing pharmaceutical quality (e.g., the New Inspection Protocol Program).

2. Pre-Approval Facility Evaluations and Inspections: An Operating Model

Pre-Approval Facility Evaluations and Inspections directly support the assessment of marketing applications by assuring that any manufacturing facility named in the application is capable of manufacturing the drug in conformance to Current Good Manufacturing Practice (CGMP) requirements and that the data submitted in the application are accurate and complete.

- **Pre-Approval Facility Evaluations are led by CDER with ORA participation[3].** This type of 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[4,5] are led by ORA with CDER participation[3].** This type of inspection directly supports 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.

2.1 Planning the Strategy for the Inspection

A Pre-Approval Facility Evaluation is initiated in conjunction with the submission of a marketing application for a drug product. At the time of submission, an Integrated Quality Assessment (IQA) Team is assembled to perform the quality assessment of a particular marketing application. The IQA Team provides aligned, patient-focused, and risk-based drug product quality recommendations inclusive of drug substance, drug product, manufacturing, and facilities. The unifying hallmark of IQA is the integration of the facility evaluation and inspection and review roles in the application assessment process. ORA investigators are fully apprised of any issue uncovered by CDER reviewers, and vice versa. The IQA Team, led by an Application Technical Lead and managed by a Regulatory Business Project Manager, consists of a drug substance reviewer, a drug product reviewer, a process/facility assessor, and, for Pre-Approval Inspections, an ORA representative(s). It may also include other roles, as needed[6]. The IQA Team is ultimately responsible for providing the quality recommendation for marketing applications, which 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, as applicable.

[3] SOPs will be developed to define ORA's and CDER's roles
[4] At this time, the process for Pre-Approval Inspections for biotechnology applications, where CDER currently leads many biotechnology inspections, will not change as part of this concept of operations.
[5] Certain inspections may be carried out by investigators assigned to foreign offices under the auspices of the Office of International Programs, as requested by ORA.
[6] See Attachment 1 for a summary of Integrated Quality Assessment (IQA) Team Roles and Responsibilities

The process/facility assessor from OPF performs an initial facility risk assessment based on information in the application and a site dossier provided by CDER's OS . A site dossier includes (but is not limited to) information on facility inspection history, recalls, shortages, customer complaints, foreign regulator inspection outcomes, information on submitted Field Alert Reports or Biological Product Defect Reports, submitted quality metric data if available, and a listing of all products manufactured at the site. Once the initial facility risk assessment is performed, the process/facility assessor seeks input from the IQA Team who may recommend that an inspection is needed based on their assessment of the accuracy and integrity of the information provided in the application. CDER and ORA collaborate to decide whether an on-site inspection is needed following the practices of the Pre-Approval Inspection Compliance Program[7]. OPF may also consult with OS, and/or OMQ in making a decision as to whether an on-site inspection is needed. If an on-site Pre-Approval Inspection is not deemed necessary, OPF continues to monitor the facility status as related to the pending applications. 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.

2.2 Conducting the Inspection

The ORA investigator leads the inspection with participation of CDER and may focus in the areas of concern outlined by the IQA Team. All inspection team members are responsible for preparing for, executing, and documenting the inspection, including contributing to the establishment inspection report which documents the items covered during the inspection within established timeframes. The inspection team should conduct the site inspection by following the Pre-Approval Inspection Compliance Program and should provide coverage to the areas of concern, identified by the IQA Team. The investigator, with input from the inspection team, documents objectionable findings and issues an FDA Form 483 when significant issues are identified.

2.3 Communicating the Findings of the Inspection

The inspection team provides the establishment inspection report to the IQA Team after it has been reviewed by the ORA Director of Investigations Branch or designee. The IQA Team, which for Pre-Approval Inspections includes an ORA representative, evaluates the report and addresses any outstanding issues, through regulatory meetings or an Information Request (IR), Discipline Review (DR), or Complete Response (CR) letter, and provides an overall recommendation on approvability of the application. During the facility assessment, communication may also need to be sent directly to the facility owner to resolve outstanding inspection issues, especially if the facility owner is different from the sponsor. The OPF assessor evaluates the sponsor's or facility owner's responses to questions in the IR/DR/CR and provides the final recommendation on acceptability of the facility. The IQA team provides an overall recommendation on approvability of the application following this assessment. Objectionable findings that impact marketed products are managed as described in the surveillance model.

[7] Not intended to change the current interaction between OPF and ORA Pre-Approval Managers

3. POST-APPROVAL FACILITY INSPECTIONS: AN OPERATING MODEL

Post-Approval Facility Inspections are similar to Pre-Approval Facility Inspections in that 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. Changes in perceived risk may also initiate such an inspection[8], 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 risk for a specific drug product or to determine any regulatory actions.

3.1 PLANNING THE STRATEGY FOR THE INSPECTION

The IQA Team is ultimately responsible for providing the quality recommendation for the marketing application, which may include a Pre-Approval Facility Inspection. The IQA Team, or an ORA Pre-Approval Manager in communication with the IQA Team, also determines the need for a Post-Approval Facility Inspection after or as part of the review and approval of a marketing application. The 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 deemed necessary, OPF prepares an assignment to provide suggested areas of concern during the inspection. To the extent feasible, OPF confirms that the product has reached the market after approval[9]. After the assignment is prepared, ORA schedules the Post-Approval Inspection. The ORA investigator leads the inspection team which may include individuals from CDER.

3.2 CONDUCTING THE INSPECTION

The inspection team performs the inspection following the Post-Approval Compliance Program and provides coverage in the areas of concern. When feasible, if the inspection team observes critical conditions, they are discussed with OPF, who will include OC and OS as needed, before the inspection closes. At this point, 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.

[8] For example, changes in post-approval or in the Reference Listed Drug specification

[9] For example, as reported in an Annual Report if the Post-Approval Inspection will be more than 12 months after approval of the marketing application

3.3 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[10]. 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. If the inspection expands to a Surveillance Inspection, the procedure follows that described in the surveillance model.

4. Surveillance Facility Inspections: An Operating Model

Surveillance Facility Inspections focus on facilities that manufacture[11] marketed prescription and over-the-counter monograph drug products as well as in-process materials or drug substances used in marketed drug products. This type of inspection is meant 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.

4.1 Planning the Strategy for the Inspection

OS maintains a manufacturing facility catalogue. 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 for inspection, ORA schedules Surveillance Inspections for individual sites. In advance of a scheduled Surveillance Inspection, OS prepares an up-to-date site dossier[12] which includes but is not limited to, information on facility inspection history, recalls, shortages, customer complaints, foreign regulator inspection outcomes, information on submitted Field Alert Reports or Biological Product Defect Reports, submitted quality metric data if available, and a listing of all products manufactured at the site. ORA then conducts an on-site inspection based on the Surveillance Compliance Program and quality information summarized in the site dossier.

[10] In Compliance Program 7346.843, recommendations for appropriate regulatory actions when there are significant deviations from CGMP regulations or from application commitments include "Application Integrity Policy, application withdrawal, FDA-requested recall, warning letter, seizure, injunction, and prosecution."
[11] Including processing, testing, packaging, and labeling
[12] Periodic stakeholder analysis of the site dossier program will determine the extent of use of the site dossier program

4.2 Conducting the Inspection

ORA performs the on-site inspection, though under defined circumstances CDER personnel may participate, when requested by ORA. If ORA observes critical conditions (e.g., which may result in an imminent health hazard), as appropriate and if feasible they may be discussed between ORA and OMQ before the inspection closes. The ORA Director of Investigations Branch 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.

4.3 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 informs CDER as soon as practical but at most within two days of closing the inspection that a facility is potentially OAI by entering such information into Panorama. Within 45 days of the close of a Surveillance Inspection, ORA completes the establishment inspection report, which includes electronic inspection documents, and a classification consistent with classifications currently identified in Field Management Directive (FMD) 86[13]:

- Official Action Indicated (OAI)
- Voluntary Action Indicated (VAI)
- No Action Indicated (NAI)

OAI Classification

If the facility inspection indicates an initial OAI classification, ORA conducts an initial written classification analysis and refers the matter, and electronic documents, to OMQ within 45 days of closing the inspection. OMQ makes 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). If an inspection is classified as final OAI, OMQ, solely or in collaboration with ORA, take an appropriate action within 3 months of the decisional letter. OMQ and ORA collaborate on interactions with facilities following enforcement actions. If OMQ determines 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

If the facility inspection indicates 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.

[13] CDER, with input from ORA, will develop written guidelines to define post-inspection classification and to provide guidance on a range of possible appropriate follow-up actions based on the outcome of an inspection and considering other relevant information.

4.4 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. For facilities associated with an application-based product, this analysis may also consider an applicant's history of post-approval changes, quality metric data (if available), distribution information, vulnerability for drug shortage, or other information that may indicate when follow-up engagement (such as written requests for information, or an in-person meeting) may be appropriate to minimize the potential for the facility to remain out of compliance or experience a drug shortage.

5. For-Cause Facility Inspections: An Operating Model

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.

5.1 Planning the Strategy for the Inspection

Requests for For-Cause Facility 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. For-Cause Inspection assignments intended to cover other program areas (e.g., unapproved drug and bioresearch monitoring inspections) are not covered by this operating model. Once one of these offices determines a For-Cause 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 per FMD-17, if required, ORA schedules the inspection, dependent on risk and priorities. ORA performs the on-site inspection, though CDER may participate, as requested. The inspection team develops an on-site inspection strategy based on the coverage requirements contained in the assignment.

5.2 Conducting the Inspection

The 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, to discuss whether to continue the inspection to gather additional information or to close the inspection and initiate prompt regulatory action.

5.3 Communicating the Findings of the Inspection

If objectionable conditions are observed, the investigator issues an FDA Form 483 and discusses it with the firm at the close of the inspection. Within 45 days of the close of a For-Cause Inspection, ORA completes an establishment inspection report. The inspection information includes a recommendation and electronic inspection documents which are available for review by the initiating office. ORA will not issue an FMD-145 letter without the concurrence of the initiating office. The initiating office completes a final assessment or classification in the following 45 days, involving other offices (e.g., ORA, OPF, OS, OC) as appropriate based on the inspection findings. Any follow-up actions are completed within 6 months post-inspection. Finally, OS updates the site dossier for the facility with information gained from the inspection.

6. Approvals

The signatures of the people below indicate an understanding in the purpose and content of this document by those signing it. By signing this document you indicate that you approve of the proposed project outlined in this business case. The Working Group will move to an implementation phase to fully develop the new processes and policies necessary to fully operationalize this operating model.

Approver Name	Title	Signature	Date
Janet Woodcock	Director, Center for Drug Evaluation and Research		
Melinda K. Plaisier	Associate Commissioner for Regulatory Affairs		

7. Attachments

Attachment 1: Integrated Quality Assessment: Roles and Responsibilities
Attachment 2: Flow diagrams of Pre-Approval, Surveillance, Post-Approval, and For-Cause Facility Evaluations/Inspections
Attachment 3: RACI charts for Pre-Approval, Surveillance, Post-Approval, and For-Cause Facility Evaluations/Inspections

Attachment 1: Integrated Quality Assessment: Roles and Responsibilities

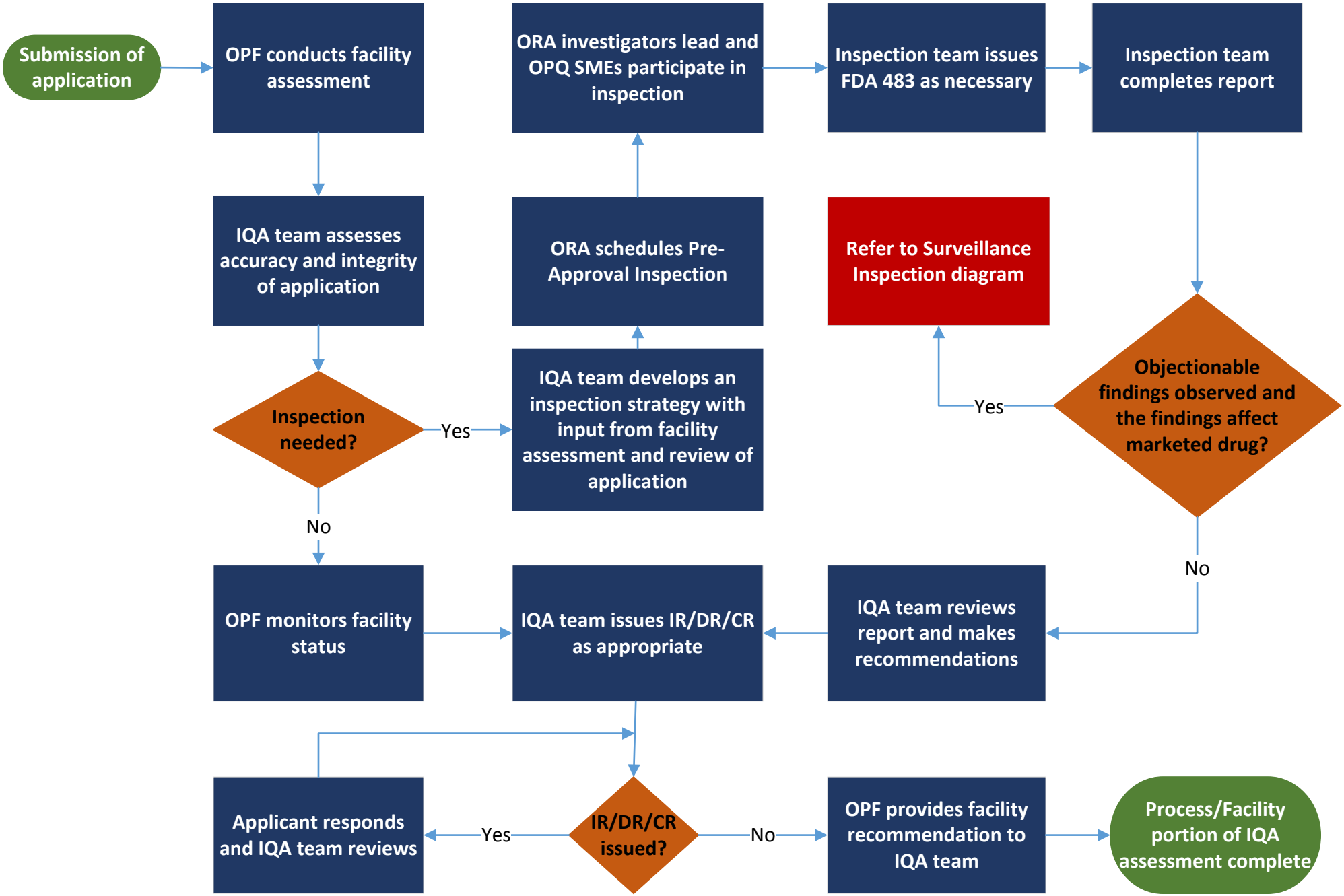
A Pre-Approval Facility Evaluation is initiated in conjunction with the submission of a marketing application for a drug product. At the time of submission, an Integrated Quality Assessment (IQA) Team is assembled to perform the quality assessment of a particular marketing application. The IQA Team provides aligned, patient-focused, and risk-based drug product quality recommendations inclusive of drug substance, drug product, manufacturing, and facilities. The unifying hallmark of IQA is the integration of the facility evaluation and inspection and review roles in the application assessment process. ORA investigators are fully apprised of any issue uncovered by CDER reviewers, and vice versa. The IQA Team, led by an Application Technical Lead and managed by a Regulatory Business Project Manager, consists of a drug substance reviewer, a drug product reviewer, a process/facility assessor from OPF, and, for Pre-Approval Inspections, an ORA representative. It may also include other roles, as needed (see Table 1). The IQA Team is ultimately responsible for providing the quality recommendation for marketing applications, which 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, as applicable.

TABLE 1. Integrated Quality Assessment (IQA) Team Roles and Responsibilities

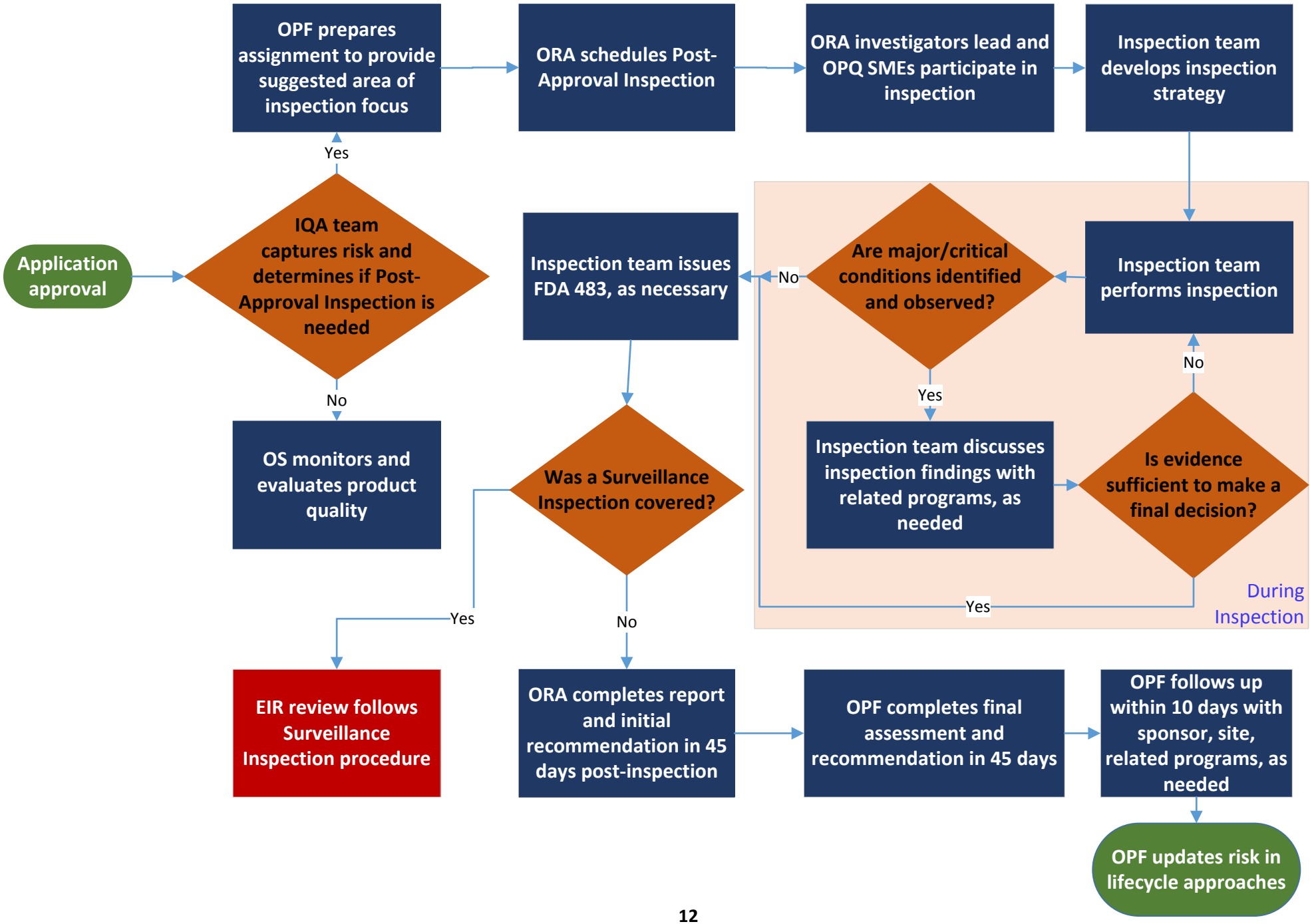
Role / Task	Responsibility in IQA Team
Scientific Content/Initial Risk Assessment	Application Technical Lead (ATL) / IQA Team
Process and Timeline	Regulatory Business Project Manager (RBPM)
Assessment of Drug Substance/Drug Master File	Drug Substance Reviewer
Assessment of Drug Product, Labeling, and Package Insert	Drug Product Reviewer
Assessment of Manufacturing Process/Facilities	Process/Facility Reviewer
Assessment of Biopharmaceutics When Needed	Biopharmaceutics Reviewer
Assessment of Microbiology When Needed	Microbiology Reviewer
Pre-Approval Inspections When Needed	ORA Investigator Leads/OPQ Reviewer(s) Participate

Attachment 2: Flow diagrams of Pre-Approval, Surveillance, Post-Approval, and For-Cause Facility Evaluations/Inspections

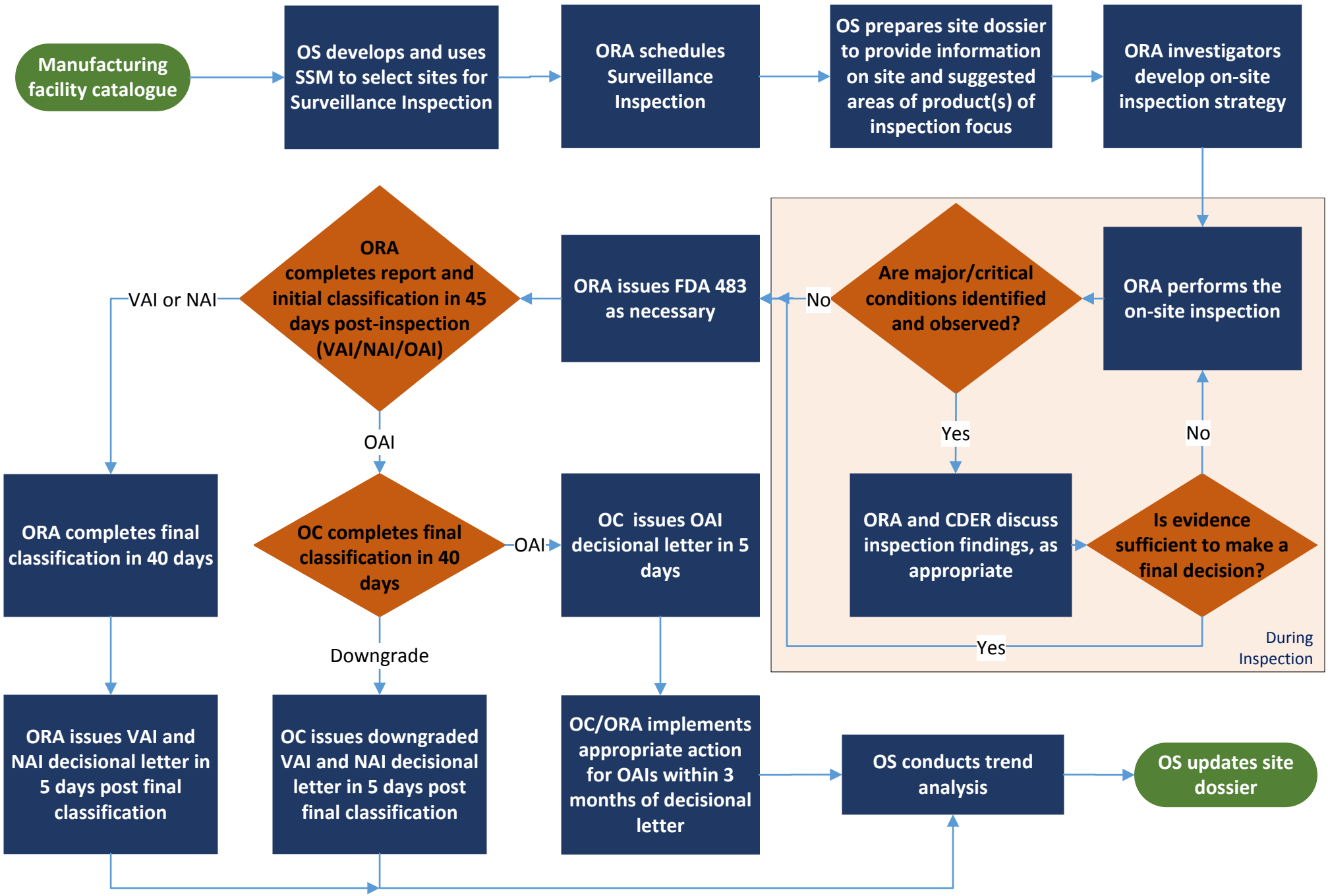
Pre-Approval Facility Inspection



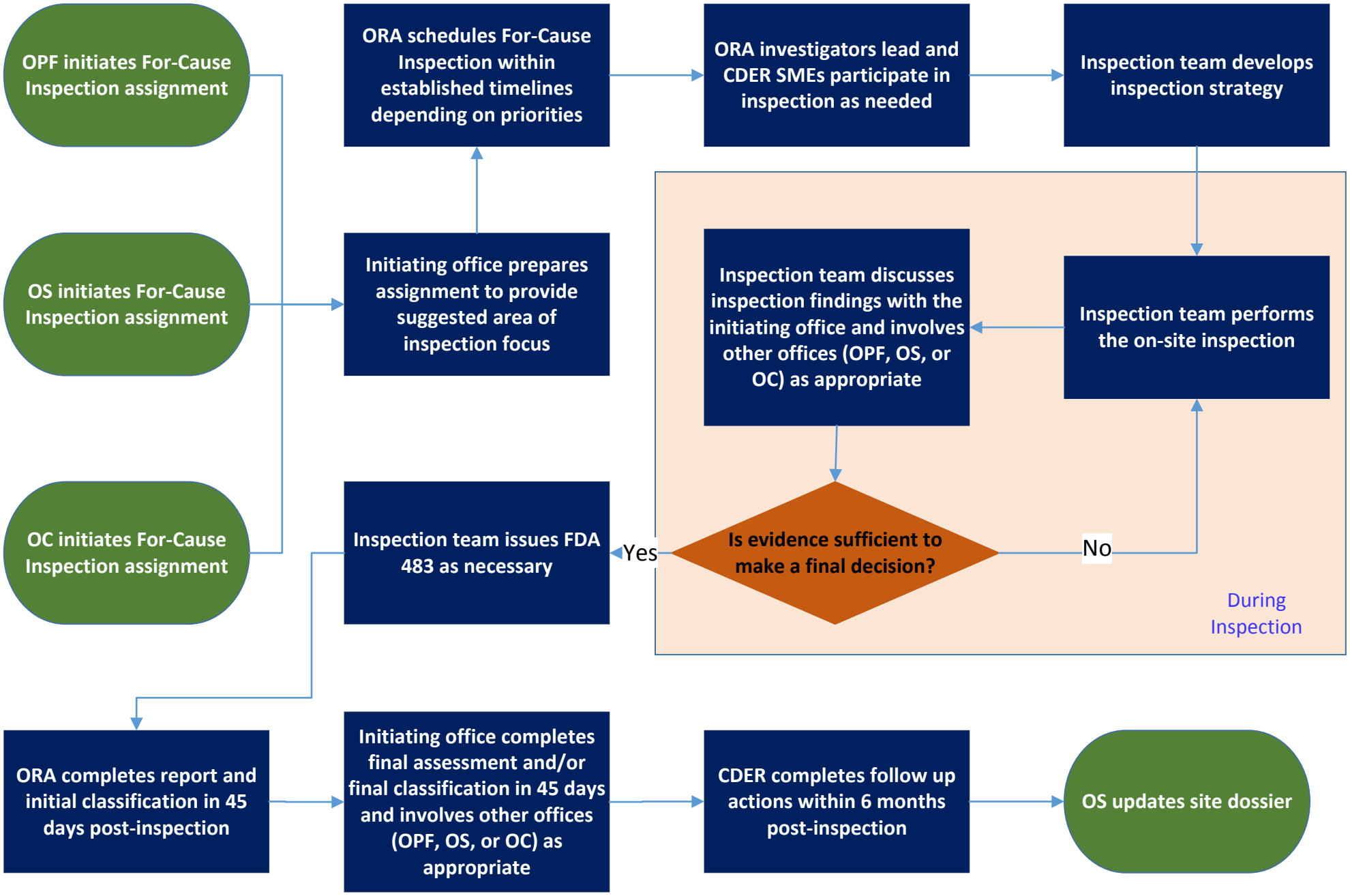
Post-Approval Facility Inspection



Surveillance Facility Inspection



For-Cause Facility Inspection



Attachment 3: RACI charts for Pre-Approval, Surveillance, Post-Approval, and For-Cause Facility Evaluations/Inspections

RACI Chart for Pre-Approval Inspection

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	

RACI Chart for Post-Approval Inspection Process

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	

RACI Chart for Surveillance Inspection

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**	

RACI Chart for For-Cause Inspection

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