CHAPTER 46—NEW DRUG EVALUATION

SUBJECT:	IMPLEMENTATION DATE:
Preapproval Inspections Revision: Compliance program revised to add elements of International Council for Harmonisation (ICH) guidances for industry *Q10 Pharmaceutical Quality System* and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*,[1] control of nitrosamine impurities, and alternative tools for evaluating facilities.	10/17/2022

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
Human Drugs Industry Codes: 50, 54–56, 59, 60–66.	**PAC**	**Subject[2]**
	46832	NDA Pre-Approval Inspection/Method Verification
	46832B	NDA Profile Sample Collection/Analysis
	46832D	PEPFAR—NDA Pre-Approval President's Emergency Plan for AIDS Relief
	46832F	NDA CMC Pilot
	46832M	Pre-License Therapeutic Biological Product Inspections
	46832P	PET NDA Pre-Approval Inspections/Investigations
	46832S	BLA Pre-License Inspections—Biosimilars
	52832	ANDA Pre-Approval Inspection/Method Verification
	52832B	ANDA Profile Sample Collection/Analysis
	52832E	PEPFAR—ANDA Pre-Approval—President's Emergency Plan for AIDS Relief
	52832P	PET ANDA Pre-Approval Inspections/Investigations
	56R927	Remote Interactive Evaluation (RIE) Activities—Human Drugs
	56R928	704a4 Activities—Human Drugs

Remarks:

1. Office of Regulatory Affairs (ORA) districts/divisions should use this revised compliance program (7346.832—*Preapproval Inspections*) for preapproval inspections (PAIs) of manufacturing facilities in support of pending drug applications.[3]

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[2] NDA=new drug application; PEPFAR=President's Emergency Plan for AIDS Relief; CMC=chemistry, manufacturing, and controls; PET=positron emission tomography; ANDA=abbreviated new drug application.

[3] In this compliance program, the synonymous terms *facility*, *firm*, *establishment, site,* and *person* cover entities subject to FDA drug manufacturing regulations and statutory authority. *Manufacturer* can differ from these terms depending on context.

2. Under this compliance program, ORA preapproval program managers (PAMs) are responsible for reporting inspectional results. ORA's Office of Pharmaceutical Quality Operations, in its Office of Medical Products and Tobacco Operations (OMPTO), maintains a list of ORA PAMs (including backup PAMs), which is published in the blue pages of the *Investigations Operations Manual* (IOM).
3. When PAI coverage is concurrent with or expanded to provide coverage of other inspection programs (e.g., compliance program 7356.002—*Drug Manufacturing Inspections*), follow the appropriate compliance programs for inspection and reporting.
4. Although this compliance program (7346.832) does not apply to the conduct of prelicense inspections (PLIs) or PAIs for biologics license applications, the reporting requirements for biologic PLIs and PAIs are in this compliance program.
5. For current good manufacturing practice (CGMP) standards concerning (a) positron emission tomography (PET) drugs, refer to 21 CFR part 212 and compliance program 7356.002P—*Positron Emission Tomography (PET) CGMP Drug Process and Pre-approval Inspections/Investigations*; (b) finished pharmaceuticals, refer to 21 CFR parts 210 and 211; (c) active pharmaceutical ingredients (APIs) in general, refer to ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*; and (d) APIs labeled as *sterile* per compliance program 7356.002A, refer to 21 CFR parts 210 and 211.
6. If an inspection is necessary to support an investigational new drug (IND), including the treatment IND, a for-cause assignment will be initiated.

FIELD REPORTING REQUIREMENTS:

1. CDER-ORA Facility Assessment Requests and Recommendations in Panorama

The Office of Pharmaceutical Manufacturing Assessment (OPMA), in the Center for Drug Evaluation and Research's (CDER's) Office of Pharmaceutical Quality (OPQ), issues a PAI decision/recommendation or sends a request for district file review (DFR) in Panorama[4] to the ORA PAM (see Part II in this compliance program). The ORA PAM responds to the request using the District Office Decision/Request task within 10 business days.

2. Instructions for Firm Responses

The investigator instructs the firm's management to submit Form FDA 483 responses to the designated ORA division, with a copy to the lead investigator.

The ORA PAM reviews the PAI portion of Form FDA 483 responses and, if inadequate, provides comments and the initial recommendation via the DO Recommendation task in Panorama.[5]

ORA provides firm responses and ORA division comments regarding those responses to OPMA.

[4] Panorama is a component of the CDER Informatics Platform that is used to manage workflow and documents.

[5] DO=district office.

3. Communication of Inspectional Results[6]

   - The investigator communicates concerns related to the PAI within 2 business days of closing the inspection and provides Form FDA 483 (if issued) with an initial field recommendation to the ORA PAM.
   - The investigator is expected to complete the establishment inspection report (EIR)—which includes the coversheet, attachments, and exhibits—in eNSpect within established ORA time frames. The investigator informs the ORA PAM upon completing the EIR.
   - ORA notifies OPMA via the CDER PAI program mailbox (cderpaiprogram@fda.hhs.gov) when the EIR is available in FDA's electronic repository systems or provides OPMA with available information about the inspection if the EIR is unlikely to be completed by 1 month before the OPQ application action date.

4. Facility Recommendations

   - The ORA PAM ensures that the tasks assigned in Panorama are completed sequentially.
   - The ORA PAM (or designee) enters the appropriate recommendation into Panorama as soon as possible after the inspection, but no later than 20 business days after the close of the inspection. However, the recommendation must be entered before the user fee date.
   - If the recommendation cannot be made until the EIR is completed,[7] the ORA PAM provides comments within the DO Recommendation task, and upon completion of the EIR, enters the recommendation.
   - The ORA PAM summarizes the rationale for the recommendation using the comments field or associated dropdown selections in Panorama.
   - The ORA PAM recommends **approve** in Panorama when none of the criteria for withholding apply (see Part V in this compliance program). The ORA PAM recommends **withhold** in Panorama when there are significant findings (see Part V) or when there is information that, in the ORA division's judgment, warrants further evaluation by CDER before recommending approval of the application.
     - When ORA finds that the "establishment is not doing the function that it is responsible for as stated in the application" or the "establishment is not ready for inspection," the ORA PAM submits the written documentation that was obtained by the investigator or received from a responsible official at the establishment to support a **withhold** recommendation.
   - For a **withhold** recommendation, the ORA PAM:
     - Emails CDERPAIprogram@fda.hhs.gov of the ORA division's decision to make a **withhold** recommendation along with Form FDA 483 as soon as possible. In those rare situations when ORA conducts PAIs for biologics license applications, the ORA PAM also emails CDERBIOTECHINSPECT@fda.hhs.gov.

[6] With regard to CDER-led PLIs and PAIs for biologics license applications, the ORA PAM is not responsible for reporting inspectional results.

[7] **Withhold** recommendations based solely on a draft EIR should be a rare occurrence.

- Enters appropriate updates into Panorama if follow-up activities have changed the **withhold** recommendation (i.e., the Form FDA 483 response is found to be adequate or a follow-up PAI is performed).

5. Facility Alerts

- Do not enter a potential Official Action Indicated (pOAI) alert in Panorama solely because of violative PAI coverage under compliance program 7346.832 during which no marketed product was covered.
- If marketed products are also covered under compliance program 7356.002, and the surveillance part of the inspection is likely to result in an Official Action Indicated (OAI) status, enter a pOAI alert into Panorama, as soon as practical, as described in the Field Reporting Requirements section of compliance program 7356.002.

6. Firm Profile Class Code Updates

In general, ORA manages the status (acceptable or unacceptable) of profile class codes covered during establishment inspections in accordance with Exhibit 5-14.6.3, Pre-Approval Inspections, in the IOM.

- Profiles are **not updated** for product-specific PAIs (no CGMP surveillance inspection (compliance program 7356.002) conducted) unless the PAI covers a new profile.
- For a PAI of an establishment with a new profile, the new profile can be added and made acceptable if the inspection is classified as No Action Indicated (NAI) or Voluntary Action Indicated (VAI) and an **approve** recommendation for the application is made.
- If an initial PAI of a new profile results in a **withhold** recommendation (the establishment inspection is classified as OAI), ORA does not enter profile information. This ensures the product cannot be marketed in the United States until a follow-up inspection verifies implementation of appropriate corrective actions or until corrections are substantially verified through other appropriate means.

7. Sample-Related Reporting Requirements

The Division of Pharmaceutical Analysis in OPQ's Office of Testing and Research (OPQ/OTR/DPA) as well as ORA laboratories perform testing on samples collected (method verification[8] and profile). If an official sample is collected at an establishment, the investigator should use the appropriate product/assignment codes (PACs) for method verification or profile analyses.

The analyzing laboratory (OPQ/OTR/DPA or ORA/Office of Regulatory Science (ORS)) maintains completed analytical worksheets. OPQ/OTR/DPA enters the laboratory results for method verification samples for a new drug application (NDA) or abbreviated new drug application (ANDA) into Panorama. The analyzing laboratory forwards a copy of the laboratory results to the CDER or ORA office that requested or collected samples.

[8] Method verification samples are collected at the manufacturing establishment on a for-cause basis and are independent of the method verification samples that may or may not have been requested directly from the ANDA/NDA applicants under the Method Verification Program, which is managed by OPQ/OTR/DPA.

The analyzing laboratory reports adverse findings by emailing a copy of the worksheet to the following recipients:

- The ORA program division for the manufacturing facility, if applicable.
- The OPQ drug substance assessor or drug product assessor assigned to the submission.

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PART I—BACKGROUND

The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that FDA may approve an NDA or ANDA if, among other requirements, the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate to ensure and preserve its identity, strength, quality, and purity.[9]

In 2002, FDA announced a significant initiative called Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century to enhance and modernize the regulation of pharmaceutical manufacturing and product quality.[10] This initiative, now called Pharmaceutical Quality for the 21st Century, encourages implementation of risk- and science-based approaches that focus FDA attention on critical areas to promote better and more consistent decisions among regulators. In accordance with the initiative, this compliance program includes scientific, risk-based approaches that incorporate inspection of the firm, including an assessment of process and product understanding and an evaluation of the firm's manufacturing readiness, its conformance with application commitments, and the reliability of data generated at the site.

As part of FDA's continued efforts to advance the Pharmaceutical Quality for the 21st Century initiative, the Agency pursues strategies to encourage a modern, risk-based pharmaceutical quality system (PQS). Mature quality practices that exceed CGMP requirements are indicative of an advanced PQS, which leads to sustainable compliance and a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight. This compliance program allows FDA to assess certain aspects of a firm's PQS and gain insight into the firm's established processes for continual system improvements.

To facilitate the management of postapproval chemistry, manufacturing, and controls (CMC) changes in a more predictable and efficient manner, FDA published the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and its *Annexes* and the draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (ICH Q12 implementation guidance) in 2021.[11] When used jointly with increased product and process knowledge—and in the context of the risk management principles in ICH guidance for industry *Q9 Quality Risk Management* and an effective PQS as described in ICH Q10—these guidance documents should enhance industry's ability to manage CMC changes effectively with less need for extensive regulatory oversight before implementation.

For example, any change to an established condition (EC)—legally binding information considered necessary to ensure product quality—requires a submission to FDA (PAS, CBE-30, CBE-0, or annual report) as detailed in the regulations (e.g., 21 CFR 314.70 and 314.97).[12] Although these regulations do not explicitly specify what constitutes an EC, they do set forth a risk-based paradigm for reporting changes. In addition, existing FDA guidance documents on postapproval changes provide

[9] See sections 505(d) and 505(j)(4)(A) of the FD&C Act (21 U.S.C. 355(d)(3) and (j)(4)(A)).

[10] See FDA, 2007, *Pharmaceutical Quality for the 21st Century—A Risk-Based Approach: Progress Report,* https://www.fda.gov/about-fda/center-drug-evaluation-and-research/pharmaceutical-quality-21st-century-risk-based-approach-progress-report.

[11] When final, the ICH Q12 implementation guidance will represent FDA's current thinking on this topic.

[12] PAS=prior approval supplement; CBE=changes being effected.

recommendations for how to report a broad set of postapproval changes.[13] ICH Q12 and the ICH Q12 implementation guidance provide an opportunity for applicants to specifically define ECs and gain clarity around which elements of the product, manufacturing process, facilities and equipment, and control strategy in their applications are considered to be ECs and therefore require reporting if changed. Proposing ECs in the application is entirely voluntary. If specific ECs are not proposed, ECs would be those (e.g., parameters, attributes, controls, specifications, facilities, and other elements necessary to ensure product quality) that FDA typically considers to be ECs based on the risk-based paradigm set forth in the regulations and the recommendations contained in guidance regarding postapproval changes.

Any ECs identified in an application, and any proposed reporting categories for changes in those ECs, are evaluated by the CDER members of the integrated quality assessment (IQA) team. In assessing specific ECs and reporting categories, the IQA team will consider areas that may need to be covered on a PAI, such as information about the PQS at establishments where the ECs will be implemented as well as the applicant's scientific justification, which can include development studies. For example, an effective PQS as described in ICH Q10 is critical for the use of the tools described in ICH Q12. An evaluation of a firm's change management system, as part of the PQS, helps to ensure that there will be appropriate reporting of changes in ECs, including that the reporting is consistent with any product lifecycle management (PLCM) document in the application. In all cases, changes are to be appropriately identified and implemented in accordance with CGMP requirements.

Further, to facilitate FDA's initiative to enhance the regulation of pharmaceutical manufacturing and product quality, FDA has developed additional tools to augment its regulatory oversight. As a result of the Coronavirus Disease 2019 (COVID-19) public health emergency, FDA has relied on various alternative tools to advance its regulatory responsibilities. This may include the following: (1) requesting existing inspection reports from trusted foreign regulatory partners through mutual recognition agreements (MRAs) and other confidentiality agreements;[14] and (2) conducting remote regulatory assessments (RRAs),[15] including (a) requesting records and other information directly from facilities and other inspected entities related to the application under section 704(a)(4) of the FD&C Act, and (b) conducting remote interactive evaluations (RIEs) where appropriate. As described further in relevant Agency policies and in this compliance program (including Attachment A), FDA may, under certain circumstances, use these tools to evaluate facilities and support regulatory decisions on applications.

The Prescription Drug User Fee Act of 1992 (PDUFA I), most recently authorized as PDUFA VI in 2017, authorizes FDA to collect user fees to fund the process for the review of human drug applications. In conjunction with the most recent reauthorization, FDA agreed to meet certain

[13] See, e.g., FDA's Scale-Up and Postapproval Changes (SUPAC) guidances and the guidances for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*, *Changes to an Approved NDA or ANDA*, and *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports*.

[14] For existing FDA MRAs with the European Union and the United Kingdom, this includes the use of official inspection reports issued by a recognized authority for manufacturing facilities located inside and outside the territory of the issuing authority. For more information, see https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra.

[15] An RRA is an examination of an FDA-regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements. RRAs assist in protecting human health, informing regulatory decisions, and verifying certain information submitted to the Agency.

performance goals intended to ensure that applications are reviewed in a timely manner. The Generic Drug User Fee Amendments (GDUFA I) of 2012, amended the FD&C Act to authorize FDA to assess and collect user fees to provide the Agency with resources to help ensure patients have access to quality, affordable, safe, and effective generic drugs. In conjunction with the most recent reauthorization of GDUFA program (as GDUFA II in 2017), FDA agreed to performance goals and program enhancements regarding aspects of the generic drug assessment program. Availability of generic drugs represents an important FDA goal in providing the American public with greater access to affordable medicines.[16]

FDA components involved in this compliance program—CDER's Offices of Pharmaceutical Quality (OPQ) and Compliance (OC), ORA division offices, and FDA laboratories—are committed to coordinating efforts and communications to address outstanding quality issues and to ensure that the above PDUFA and GDUFA performance goals are met. In 2017, CDER and ORA entered into an agreement, *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations* (ConOps),[17] which outlines the roles and responsibilities of CDER and ORA for facility evaluation and inspections (preapproval, postapproval, surveillance, and for-cause) for human drugs. This compliance program supports ConOps and fosters the integration of facility evaluations (or application assessments) and PAIs. For more information on how quality risks could be addressed through integration of application assessments and PAIs, see Attachment B.

[16] For more information about PDUFA VI and GDUFA II, see Pub. L. 115-52, FDA Reauthorization Act of 2017, and the FDA User Fee Programs web page at https://www.fda.gov/industry/fda-user-fee-programs. The current legislative authority for PDUFA and GDUFA expires in September 2022. For information about reauthorization activities, see the PDUFA VII web page at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027 and the GDUFA III web page at https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii.

[17] See https://www.fda.gov/drugs/pharmaceutical-quality-resources/integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept-operations.

PART II—IMPLEMENTATION

1. Scope

Preapproval facility evaluations and inspections support the assessment of marketing applications by ensuring that any establishment named in or referenced in support of an application can perform the proposed manufacturing operations in conformance with CGMP requirements and that data submitted in the application are accurate and complete.

- **Preapproval facility evaluation:** CDER, with ORA participation, considers information about each facility named in a marketing application, the drug being manufactured, and other information in the application to determine whether a PAI is needed before the application can be approved from a quality perspective.
- **Preapproval inspection:** ORA, with CDER participation, evaluates the adequacy of the manufacturing processes and control strategy to ensure commercial product quality and conformance to application, facility, and CGMP requirements. CDER uses information from the inspection in conjunction with other information to determine whether to approve a drug application.

This compliance program also provides risk-based strategies for the scope of inspectional coverage and clarifies roles to establish efficient communication. During the PAI, if necessary (e.g., systemic CGMP deficiencies are discovered), the scope of the inspection can be expanded to add coverage under compliance program 7356.002.

2. Strategy

A. Risk-Based Determination for PAI

This revised compliance program reinforces FDA's risk-based approach to determine whether inspections are needed using information provided in applications and information FDA may have regarding the facilities. If FDA finds that sufficient information is available, a PAI may not be needed. When a marketing application is submitted, CDER initiates the preapproval facility evaluation by assembling an IQA team to perform the quality assessment. The IQA team provides patient-focused and risk-based quality recommendations relating to the drug product, including recommendations for facilities that manufacture, process, package, or hold and test the drug product[18] or drug substance.[19] The team, led by an application technical lead and managed by a regulatory business project manager, consists of a drug substance assessor, drug product assessor, OPMA manufacturing assessor, and ORA representative(s). Additional assessors may be assigned as appropriate.[20]

[18] See 21 CFR 210.3(b)(12).

[19] See ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, page 41.

[20] Supplements are assessed by an application assessment team, which may not involve team members that would typically be assigned to an IQA team. For ease of reference, this compliance program uses *IQA team* throughout.

In performing the quality assessment, the IQA team determines the need for PAIs of facilities listed in the application by assessing:

- Product risk and manufacturing (process and facility) risks.
- The accuracy and reliability of the information provided in the application.

Product knowledge and risk assessments focus on understanding the risks associated with a product's critical quality attributes (CQAs) in the specific product's context of use (e.g., therapeutic index, patient population, clinical benefit). Drug product design helps to determine whether the product can meet patients' needs and maintain its intended performance through its proposed shelf life.

Manufacturing process risk assessments focus on understanding the impact of the process on the product's CQAs. A process is generally considered well-understood and controlled when (1) critical sources of variability are identified and explained, (2) variability is managed by the process at all scales, and (3) process performance and product quality attributes can be adequately and reliably controlled.

Good product and process understanding means that characteristics critical to quality from the patient's perspective have been identified and translated into the product's CQAs and that material attributes and process parameters that affect the CQAs have been identified, characterized, and are controlled.

Manufacturing facility risk assessments focus on the demonstrated capabilities of the manufacturing or testing facilities and their relevance to the marketing application. They include, but are not limited to, reviews of the facility's recent manufacturing history through the evaluation of EIRs and exhibits, applicable product defect reports (e.g., field alert reports (FARs), MedWatch reports), associated recalls, regulatory actions, and available foreign regulatory reports.[21]

The assessment of the accuracy and integrity of the information from a site, in support of the application, is also an important factor in determining the need for a PAI. A PAI can be triggered when there is a need to confirm the accuracy and reliability of the quality data, which is critical in determining the safety, efficacy, and quality of the drug product. Additionally, a PAI can be triggered to confirm that a facility's operations match those proposed in the application.

In conclusion, the IQA team determines the need for PAIs based on the cumulative risk assessment of the application. Alternative tools may be used in lieu of or in advance of a PAI (see Attachment A for RRAs).

[21] For information on FDA's MRAs, see https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra.

B. Inspection by Objective

There are four primary inspectional objectives for PAIs, each of which requires strategies that consider the concerns and potential risks identified during the IQA team's application assessment and facility risk assessment:

- **Objective 1: Readiness for Commercial Manufacturing.**
- **Objective 2: Conformance to Application.**
- **Objective 3: Data Integrity Audit.**
- **Objective 4: Commitment to Quality in Pharmaceutical Development.**

PAI coverage is based on the totality of information available to FDA about the site, which can include information from previous inspections of the establishment. FDA uses a holistic approach to identify risks that should be evaluated during an inspection (e.g., the facility's role in the application, previous inspection history of the facility, complexity of the manufacturing process, information obtained through the use of alternative tools). For further details on inspectional and auditing techniques related to these objectives, refer to Part III—Inspectional—of this compliance program. The performance and documentation of a comprehensive PAI may be facilitated by the use of applicable eNSpect inspection protocols.

Some objectives may need to be covered on every inspection. The investigator determines the areas of coverage during the PAI with input from members of the IQA team, as applicable. This input must be provided in writing (e.g., via email) before the inspection and may include the risks identified by the IQA team during its application assessment. The depth of coverage of each objective may vary depending on the risk identified. If significant issues are observed during the PAI, this compliance program allows for adjustments to the inspectional strategy (e.g., expanding the PAI coverage to add coverage under compliance program 7356.002). The following table illustrates coverage considerations for each objective of this compliance program.

Objective	**Coverage**
Objective 1 Readiness for Commercial Manufacturing	
Objective 1a: Manufacturing and laboratory capabilities, changes, deviations, and trends relating to the development of drug substances and drug products have been adequately evaluated to ensure readiness for manufacturing.	Cover on every PAI.
Objective 1b: A sound and appropriate program for sampling, testing, and evaluating components (including APIs), in-process materials, finished products, containers, and closures for purposes of releasing materials or products has been established, including a robust supplier qualification program.	When determining whether to cover, consider risk factors such as: • The application assessment identified issues in these areas. • Previous facility information (e.g., previous inspections, RRAs) identified issues in these areas.

Objective	Coverage
Objective 1c: Sufficient facility and equipment controls are in place to prevent contamination of and by the application product (or API).	When determining whether to cover, consider risk factors such as: • The facility has never been inspected. • A new building has been added that has never been inspected. • The equipment is new or has not been covered on a previous inspection. • The facility has undergone major changes since the last inspection. • The product requires special containment or separation. • The application assessment identified issues in these areas. • Previous facility information (e.g., previous inspections, RRAs) identified issues in these areas.
Objective 1d: Adequate procedures exist for batch release, change management, and investigating failures, deviations, complaints, and adverse events, and for reporting this information to FDA (e.g., through FARs).	When determining whether to cover, consider risk factors such as: • There is no history of prior coverage of these elements. • The quality system has changed since the last inspection. • Previous facility information (e.g., previous inspections, RRAs) identified deficiencies in these areas.
Objective 1e: The proposed commercial process and manufacturing batch record, including instructions, processing parameters, and process control measures, are feasible and scientifically and objectively justified. This objective is linked to the firm's process validation program across the product lifecycle.	Cover on every PAI. The depth of coverage will vary based on the extent of process validation activities and any application assessment issues identified at the time of the inspection.
Objective 2 Conformance to Application	Cover on every PAI.
Objective 3 Data Integrity Audit	Cover on every PAI. The depth of coverage will vary depending on the inspectional findings.
Objective 4 Commitment to Quality in Pharmaceutical Development	Cover: • On the initial PAI. • Periodically on subsequent PAIs, with frequency based on risk. • When there have been major changes to the quality system, management team, or corporate structure. The depth of coverage will vary based on the risk and application-specific issues identified.

3. Program Management Instructions

A. NDA/ANDA Facility Evaluation and Inspection

Within 60 calendar days[22] of receiving an NDA or ANDA, OPMA sends a PAI or DFR request to ORA or enters a facility recommendation via Panorama.

For PAI requests:

- OPMA requests the PAI through the OPMA Decision/Request task with clear justification and provides specific information on the inspectional strategy regarding the risk and concerns identified.
- ORA evaluates the request, schedules the inspection, and notifies OPMA. To the extent possible, ORA and CDER collaborate on the planning and timing of application assessment and inspectional activities. If ORA's evaluation suggests that a PAI is not warranted, a final determination is made in collaboration with OPMA. Within 10 business days of receiving the request, the ORA PAM enters the reason for not initiating the inspection in Panorama, along with ORA's recommendation.
- ORA leads the inspection and CDER participates with appropriate (CDER and ORA management) concurrence.
- The inspection team reports its findings and provides recommendations via the ORA PAM to OPMA. All participants on the inspection team (CDER and ORA) are responsible for submitting their portion of the EIR and supporting exhibits to the lead investigator.
- OPMA evaluates the inspection team's results within the context of the application and communicates relevant findings or concerns to the IQA team.
- For PAI **withhold** recommendations from ORA or significant deficiencies noted by OPMA, OPMA evaluates the inspection team's findings and the firm's response and makes the final recommendation on the adequacy of the firm for the covered PAI and application. OPMA communicates the final recommendation (concurrence/nonconcurrence) to ORA.

For DFR requests:

- OPMA requests a DFR through the OPMA Decision/Request task.
- ORA has 10 business days to respond by entering *approve facility*, *withhold approval*, or *PAI*. The decision to initiate a PAI following a DFR is made in collaboration with OPMA. When a PAI is indicated, the program management instructions above apply.
- For **withhold** recommendations, ORA communicates the rationale for the recommendation to OPMA. OPMA evaluates the rationale and makes the final recommendation regarding the firm's adequacy for the covered PAI and application. OPMA communicates the final recommendation (concurrence/nonconcurrence) to ORA.

[22] In some cases, OPMA may request a PAI after 60 days based on the IQA team's further assessment of the application. To the extent possible, OPMA will avoid delays in requesting PAIs to ensure timely reporting of inspectional outcomes. In addition, a delay in the PAI request beyond 60 days may then delay ORA's ability to submit the EIR to CDER for review by 1 month before the OPQ application action date.

B. Scheduling and Preparation

A PAI should be requested and performed at the earliest opportunity, well before the user fee goal date. When scheduling the PAI, ORA should (1) consider the benefit to the application assessment process of resolving concerns observed during the PAI, and (2) allow sufficient time for the firm and applicant to addresses such concerns after the PAI.

A PAI may be scheduled with other inspection programs for efficient inspectional coverage. ORA division management may add a systems-based CGMP inspection pursuant to compliance program 7356.002 under specific circumstances, such as when:

- The establishment is on CDER's site surveillance inspection list from the risk-based site selection model.[23]
- A for-cause inspection has been issued.
- Findings from the PAI indicate the need for coverage of marketed products.

ORA may choose to contact establishments before a PAI is conducted. If FDA determines that it is necessary to conduct the inspection at a time when the product identified in the application is being manufactured, FDA will notify the facility so that there is sufficient time for the facility to adjust its manufacturing schedule as needed. For original NDAs, FDA's goal is to provide this notification at least 60 days in advance of the PAI and no later than midcycle.[24]

For any application, FDA reserves the right to conduct manufacturing facility inspections at any time during the review cycle, whether or not FDA has communicated to the facility the intent to inspect. If inspectional planning has started and the establishment is not ready for inspection, the establishment should provide a written explanation and the date when it will be available for inspection.[25]

Any postponement of a scheduled inspection by the establishment or applicant should be reported to OPMA promptly, as should any delays in gaining access to records or information that could affect FDA's time frames for assessing an application.[26]

CDER should prepare for a PAI by conducting the following activities:

- The IQA project manager invites the ORA PAM, investigator, or division designee to participate in IQA meetings on the application.
- The OPMA manufacturing assessor collects inspectional concerns from the IQA team and communicates these concerns to the ORA PAM and investigator in writing. The OPMA manufacturing assessor provides insights and advice about covering these concerns on-site, which the investigator can use to develop an inspection plan.

Investigators should prepare for a PAI by conducting the following activities:

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[23] See MAPP 5014.1 *Understanding CDER's Risk-Based Site Selection Model,* https://www.fda.gov/media/116004/download.

[24] See the PDUFA VII commitment letter, https://www.fda.gov/media/151712/download.

[25] The written response should be from a responsible official at the facility or a designee.

[26] Follow existing procedures (e.g., IOM) for documentation and referral of refusals of access to information during inspection.

- Become familiar with the CMC section of the application and related drug master files (DMFs) for the establishment to be inspected. If possible, review the pharmaceutical development section before initiating the inspection.
- Participate as appropriate in IQA meetings to provide or seek feedback on the application. Also, as necessary, discuss questions/concerns related to data reliability (e.g., test methods, data tables, raw material attributes, justifications for finished specifications) with the appropriate IQA team members. Determine if other IQA team members need data audit coverage of specific areas during the inspection.
- Contact the OPMA manufacturing assessor with questions about the subject application when planning inspectional coverage. (This activity can be conducted by the ORA PAM, investigator, or a designee.)
- Develop an inspection plan with other inspection team members that is specific to the establishment and product being inspected and consistent with this compliance program's objectives and inspectional and data auditing techniques. Review the history of the firm and Form FDA 483 observations from previous inspections.

Applications often contain trade secrets or confidential commercial information, and it is essential that the information be carefully protected to prevent its release outside FDA. Divisions are expected to establish a controlled access filing system to prevent the unauthorized use or release of application information.

C. Inspection Team

ORA leads PAIs for NDAs and ANDAs, and CDER participates with appropriate (CDER and ORA management) concurrence. ORA divisions assign experienced investigators and analysts, if needed, to conduct PAIs, and they may also request support directly from other offices, national expert investigators (drugs), or the Pharmaceutical Inspectorate. Support from such additional sources is especially valuable if local resource limitations affect a division's ability to perform the PAI. Team members conducting PAIs should have appropriate training and experience.

4. Importance of Application Assessment Integration

Achieving a science-based approval decision about each application from a pharmaceutical quality perspective requires an integrated assessment of the application and associated facilities. Because this requires input from multiple disciplines in FDA, differences of opinion may occur. FDA offices involved in the PAI program are covered by an equal voice philosophy. Under this philosophy, all appropriate expertise should be considered in the important decisions made about applications, and the perspective from each FDA office assigned a role in reviewing and evaluating drug applications is valuable. This equal voice environment is achieved, in practice, when each organizational unit:

- Integrates each contribution to enhance the decision of the multidisciplinary team.
- Provides an environment in which all team members can express their views for the areas in which they have a recognized responsibility.

- Ensures an avenue for promptly raising unresolved differences of opinion through the management chain for prompt resolution.
- Maintains transparency with a full and adequate record documenting decisions, including significantly differing views.

PART III—INSPECTIONAL

1. NDA/ANDA Inspectional/Audit Coverage, Objectives, and Techniques

The type and depth of inspectional/audit coverage needed to address each PAI objective is described in this section, along with appropriate regulatory citations.

A. Summary of Objectives

(1) Objective 1: Readiness for Commercial Manufacturing

Determine whether the establishment has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.[27]

- **Objective 1a:** Manufacturing and laboratory capabilities, changes, deviations, and trends relating to the development of drug substances and drug products have been adequately evaluated to ensure readiness for manufacturing.
- **Objective 1b:** A sound and appropriate program for sampling, testing, and evaluating components (including APIs), in-process materials, finished products, containers, and closures for purposes of releasing materials or products has been established, including a robust supplier qualification program.
- **Objective 1c:** Sufficient facility and equipment controls are in place to prevent contamination of and by the application product (or API).
- **Objective 1d:** Adequate procedures exist for batch release, change management, and investigating failures, deviations, complaints, and adverse events, and for reporting this information to FDA (e.g., through FARs).
- **Objective 1e:** The proposed commercial process and manufacturing batch record, including instructions, processing parameters, and process control measures, are feasible and scientifically and objectively justified. This objective is linked to the firm's process validation program across the product lifecycle.

(2) Objective 2: Conformance to Application

Verify that the formulation, manufacturing, or processing methods; analytical (or examination) methods; and batch records are consistent with descriptions contained in the CMC section of the application. This may include CMC information relevant to exhibit batches, biobatches, other pivotal clinical batches, and the proposed commercial-scale process.

[27] When conducting PAI for PET products only, please also refer to compliance program 7356.002P—*Positron Emission Tomography (PET) CGMP Drug Process and Pre-approval Inspections/Investigations* for Objective 1 coverage.

(3) Objective 3: Data Integrity Audit

Audit and verify raw data at the facility that are associated with the product. This information can, among other things, help to authenticate the data submitted in the CMC section of the application as relevant, accurate, complete, and reliable for CDER assessment.

(4) Objective 4: Commitment to Quality in Pharmaceutical Development

Assess the pharmaceutical development program by evaluating the extent to which it is supported, defined, managed, and continuously assessed for its effectiveness as well as its use in supporting continual improvement of the PQS.

B. Detailed Description of Objectives

(1) Objective 1: Readiness for Commercial Manufacturing

Determine whether the establishment has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations.

(a) Objective 1a: Manufacturing and laboratory capabilities, changes, deviations, and trends relating to the development of drug substances and drug products have been adequately evaluated to ensure readiness for manufacturing.

Development of sound manufacturing and laboratory operations for an application product includes repeated, sequential activities that should build understanding of the operational failure modes. Developing this understanding and making adequate improvements is critical to ensure readiness for manufacturing. To evaluate capabilities, assess whether events and investigations relevant to the proposed commercial manufacturing process have been appropriately evaluated, including related laboratory, equipment maintenance, and manufacturing (e.g., development batch) investigations. Investigative reports or resultant change control reports for development issues may not always be as comprehensive as required for marketed drugs. Nonetheless, the firm should appropriately document, record, and objectively assess all development data and information, including but not limited to data submitted in or generated after the filing of an application or DMF. The firm should effectively manage and apply product and process knowledge gained throughout the development and commercial life of the product, as appropriate. Effective knowledge management assists in risk identification and supports risk management.[28]

Examples of deviations related to the drug named in the application include:

- Laboratory issues that occurred during or after method validation, such as:

[28] Knowledge management is a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components. Sources of knowledge include, but are not limited to, prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities. See ICH Q10.

  - Unexpected laboratory events—including results that fall outside of the specifications or acceptance criteria—identified during stability, in-process, and release testing for the exhibit batches, biobatches, or process validation batches.
  - Discrepancies found while conducting the method validation (particularly issues that may have occurred in its final stages) or technical transfer.
  - Changes in an analytical method after completing the method validation or technical transfer because of an inability to use the method as written.
- Related equipment maintenance and performance issues, which could affect the proposed commercial manufacturing process, such as:
  - Calibration failures associated with commercial equipment planned for use in the proposed commercial batch record.
  - CGMP investigations and trending associated with the performance and capability of the commercial equipment planned for use in the proposed commercial batch record.
  - CGMP manufacturing investigations (e.g., significant deviations, rejects, complaints/returns) and trending associated with similarly manufactured marketed drug products at the establishment.
  - Significant facility or equipment failures.

Evaluate these events or investigations to determine if the establishment is prepared for the proposed commercial manufacturing process at commercial scale, including that there are appropriate controls in place to detect and mitigate the most likely and significant problems.

Review the firm's change management system for product-specific or manufacturing-related changes implemented by the firm to confirm that there are data supporting the effectiveness of the changes. Evaluate and confirm that product changes are documented (with justification) and that quality risk management is used to evaluate proposed changes for potential risks (e.g., hazardous impurities) and their impact on product quality. Evaluate and confirm the appropriate implementation of product-specific or manufacturing-related changes, which should provide a high degree of assurance that there are no unintended consequences. It is essential that changes are implemented to correct identified process flaws and that the change management system is robust and includes assessing the need for additional validation studies for any change.[29]

Related regulations for finished pharmaceuticals: 21 CFR 211.67(a) addresses equipment maintenance, cleaning, and sanitization. For the validation/verification of analytical methods, refer to 21 CFR 211.160–211.167 and 211.194. Refer to 21 CFR 211.100, 211.192, and 211.198 for regulations relating to product deviations and investigations. Refer to 21 CFR 211.100(a) and 211.22(d) for the change management system.

Related guidance for APIs: For preventative maintenance, cleaning, and sanitization of equipment, refer to ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,* section V.B, Equipment Maintenance and Cleaning. For the validation of analytical methods, refer to ICH Q7, section XII.H, Validation of Analytical Methods. For guidance relating to product investigations, refer to ICH Q7, sections VI.E, Batch Production

[29] See ICH Q10.

Records, VI.G, Batch Production Record Review, VIII.A, Production Operations, XIII, Change Control, and XV, Complaints and Recalls.

(b) Objective 1b: A sound and appropriate program for sampling, testing, and evaluating components (including APIs), in-process materials, finished products, containers, and closures for purposes of releasing materials or products has been established, including a robust supplier qualification program.

Review sampling plans and procedures, including those described in batch records, to evaluate the establishment's intended approach to sampling components, in-process materials, and finished product. Check the sampling plans to confirm that representative samples are collected and tested/examined to verify product quality. The method of selecting samples, number of samples taken, statistical criteria for the number of samples taken, and acceptable and unacceptable quality limits should be scientifically based and appropriate. Consider the extent of experiences with the proposed commercial process when determining adequacy of sampling plans. Also, areas of criticality or process vulnerability should receive special attention because these points in a process generally require more extensive sampling. For example, a firm may consider the use of process analytical technology (PAT).[30]

For finished dosage establishments purchasing multiple lots of components[31] from an external supplier, evaluate the suppliers' variability and the specification criteria. For finished dosage and API establishments, the firm should establish statistical criteria for component, in-process, and finished product variability in comparison with the specification criteria. If the division believes that it is warranted, a for-cause sample of the component can be collected. Contact the laboratory for instructions before collection.[32]

Related regulations for finished pharmaceuticals: 21 CFR 211.160 requires sampling plans (and specifications) to be scientifically based and appropriate; 21 CFR 211.165 requires sampling plans for finished product to be in writing and to meet appropriate statistical quality control criteria before batch release; 21 CFR 211.110, 211.134, and 211.166 address sampling in the context of in-process materials, labeling, and stability, respectively; and 21 CFR 211.84 requires that sampling of components, drug product containers, and closures be representative.

Related guidance for APIs: Refer to ICH Q7, section XI.A, General Controls, which recommends sampling plans to be scientifically sound and appropriate and sampling procedures to be in writing. This section also addresses sampling in the context of raw materials, intermediates, APIs, and labels and packaging materials. ICH Q7, section VII.C, Sampling and Testing of Incoming Production Materials, recommends that samples should be representative of the batch of material from which they are taken. ICH Q7, section XI.F, Expiry and Retest Dating, addresses sampling in the context of performing a retest.

[30] See guidance for industry *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.

[31] The term *component* includes APIs, excipients, and processing aids (21 CFR 210(b)(3)).

[32] Refer to compliance program 7356.002F—*Active Pharmaceutical Ingredient (API) Process Inspection*.

(c) Objective 1c: Sufficient facility and equipment controls are in place to prevent contamination of and by the application product (or API).

Coverage of this element is warranted for new construction or facility design, new uses of existing equipment that pose potential risks (e.g., addition of a highly potent product), or equipment operations unique to the application under review. Observe the firm's operations as you inspect the facility and after reviewing blueprints, floor plans, or as-built diagrams of utility systems (such as the purified water system piping and air handling systems). Verify that the establishment has facility, equipment cleaning, maintenance, and utility system controls in place (or planned) that are designed to prevent contamination that could be deleterious to the specific application product, and ensure that controls are in place to prevent cross-contamination of and by the application product.

Inspect new construction intended for the application product, as well as the installation of new equipment, and other significant changes to the existing facility or practices relating to material/personnel flow. Evaluate the establishment's proposed compliance with related CGMP requirements. Pay special attention to the new product or marketed products that are highly potent or potentially sensitizing in humans to ensure that the product is not liable to contaminate existing products in the facility.

Related regulations for finished pharmaceuticals: 21 CFR 211.42, 211.46, 211.48, 211.52, 211.56, 211.58, 211.63, 211.65, and 211.67 require facility and equipment controls to prevent contamination and to ensure well-organized operations.

Related guidance for APIs: Refer to ICH Q7, sections IV.A (Design and Construction) through V.B (Equipment Maintenance and Cleaning), which recommend facility and equipment controls to prevent contamination and to ensure well-organized operations.

(d) Objective 1d: Adequate procedures exist for batch release, change management, and investigating failures, deviations, complaints, and adverse events, and for reporting this information to FDA (e.g., through FARs).

Review the establishment's quality and change management procedures and audit the establishment's compliance to its procedures for *already marketed product,* as appropriate (e.g., selecting actual failures, deviations, and complaint investigations; related adverse drug experience reports, including submissions to FDA if required). Note that the regulations for adverse drug experience (ADE) reporting only cover prescription and application products. If significant problems are found with the establishment's existing complaint handling and reporting procedures, the division should consider recommending a directed inspection of the ADE reporting system under compliance program 7353.001—*Postmarketing Adverse Drug Experience (PADE) Reporting Inspections*.[33]

Changes must be implemented promptly in accordance with CGMP to mitigate the risk of product quality issues to future batches (e.g., changes based on investigations, corrective actions and preventive actions (CAPAs), ongoing process performance and product quality monitoring signals).

Verify that the firm's change management system assesses the need for new or revised ECs (e.g., to respond to observed variability), and ensure the firm has procedures to conduct such assessments

[33] For further guidance, contact the Office of Scientific Investigations in CDER's Office of Compliance, the organization responsible for managing the ADE site inspection program.

and to determine appropriate reporting categories for new or revised ECs where needed (as defined by the application or existing guidance).

If the applicant proposed specific ECs in the application, note the following:

- The proposed ECs may differ from those typically considered to be ECs following the risk-based paradigm in regulations and recommendations in guidance.
- The reporting categories for those ECs can be proposed in a PLCM document. Alternatively, an applicant can decide not to include specific reporting categories for changes, but to follow the regulations and recommendations in guidance.[34]
- The OPMA manufacturing assessor (with input from other CDER members of the IQA team as needed) will communicate to the ORA PAM a written request for coverage of development studies supporting the proposed ECs as warranted before the start of the inspection.

If specific ECs are not proposed by the applicant, the ECs are those elements of the application that FDA typically considers to be ECs based on the risk-based paradigm in the regulations and recommendations contained in guidance regarding postapproval changes.

Related regulations for finished pharmaceuticals: 21 CFR 211.192 and 211.198 address failure and complaint investigations; 21 CFR 211.100 addresses deviations from written manufacturing procedures; 21 CFR 314.81(b)(1) is the requirement for submitting a FAR to FDA; 21 CFR 314.70 and 314.97 address change reporting requirements related to approved applications; 21 CFR 314.80 addresses ADE reporting requirements for application products; and 21 CFR 310.305 addresses ADE reporting requirements for marketed prescription drugs for human use without approved NDAs.

Related guidance for APIs: Refer to ICH Q7, sections VI.E, Batch Production Records, VI.G, Batch Production Record Review, VIII.A, Production Operations, XIII, Change Control, and XV, Complaints and Recalls, for guidance relating to failure and complaint investigations and deviations from written manufacturing procedures.

(e) Objective 1e: The proposed commercial process and manufacturing batch record, including instructions, processing parameters, and process control measures, are feasible and scientifically and objectively justified. This objective is linked to the firm's process validation program across the product lifecycle.

An essential part of the inspection is evaluating the justification for the proposed commercial process and the manufacturing batch record. The extent of process validation activities that have been completed at the time of application submission can vary, but, at a minimum, data from Stage I process validation should be available. To establish process feasibility, evaluate Stage I process validation development studies and knowledge gained about manufacturing operation vulnerabilities, including the influence of raw material variability, and determine the purpose of each study performed by the firm. For example, review studies conducted to establish process controls or process parameters directly related to the CQAs of the drug product in the application.[35] These may include

[34] See footnote 13.

[35] Applications for aseptic processes, sterilization processes, and certain biotech processes include summaries of process validation studies. Review the studies and include deficiencies on Form FDA 483.

studies of worst-case or boundary conditions to establish proven acceptable ranges or more sophisticated studies involving design of experiment or multivariate analysis modeling. Assess the protocols and their execution and the reliability of the data and conclusions. Include the inadequacy of data to support the filed processing approach, or the proposed master batch record provided during inspection, on Form FDA 483.

This evaluation includes a review of the firm's scale-up studies (e.g., the scale-up from the biobatch, or pivotal batches, to a larger (interim or full) scale batch). The firm may need to change its proposed commercial process as scale-up studies are completed and knowledge is gained. Such changes alone are not a violation and should not be cited as a deficiency. However, if feasible, discuss these findings with the OPMA manufacturing assessor to determine the impact of such changes on the objectives of this compliance program.

Determine and report the firm's projected timeline for completion of additional process validation activities and additional planned studies and their purpose. Though not required at the time of the PAI, completion of certain planned studies, including Stage 2 of process validation,[36] may demonstrate that the product can be reliably manufactured at commercial scale. If the firm states that it has completed the process validation activities necessary to distribute the finished drug product (i.e., completion of Stage 2, Process Performance Qualification), fully audit and assess these studies and conclusions. These include studies and experiments to scientifically optimize processing parameters and other manufacturing instructions for significant processing steps. Additional studies typically include commercial-scale batches (conformance batches) that are manufactured at the site in accordance with the master batch and production control record using qualified commercial-scale equipment and utilities and trained production personnel. These commercial-scale studies are typically conducted in accordance with a formal protocol and are intended to confirm the process design before commercial launch. They also establish a level of reproducibility and consistency at nominal processing conditions. One of the firm's conclusions from these Stage 2 process validation studies must be that a high level of assurance was achieved in that the commercial process is capable of consistently delivering quality product meeting its CQAs. Though not required at the time of the PAI, the manufacturer is expected to plan for sufficient ongoing evaluation (Stage 3, Continued Process Verification) of the manufacturing process once marketing approval has been granted by CDER.

Thoroughly examine results and data of manufactured batches to determine if unresolved issues exist with the commercial control strategy. Listed below are examples of situations requiring follow-up:

- The drug product or API does not meet its CQAs, and root cause has not been determined.
- Batch records, in-process data, or process monitoring records reveal an unexpected highly variable process and the reason is unknown.
- Inconsistent execution of the batch record and manufacturing instructions or operator workarounds (possible indication of poor process design or training).
- Control measures do not appear to align with raw development data (e.g., important parameters or material attributes that impact CQAs are not being monitored or measured at the appropriate frequency).

[36] See Part V in this compliance program.

- Sampling and monitoring plans for Stage 2 process validation (e.g., process qualification) are not justified or are insufficient based on raw development data.
- The data justifying critical process parameters are inadequate.

Review completed studies in the process validation lifecycle for related drugs to evaluate the firm's capabilities and procedures. Interviewing key employees, such as the lead validation engineer, may be helpful in assessing a firm's ability to implement a sound process and control strategy. List deficiencies in these studies on Form FDA 483, and advise the firm that appropriate corrections must be completed before commercial distribution of the first batch.

If unable to provide sufficient process validation lifecycle coverage, state as such in the inspection report. Divisions should cover these processes during the next surveillance or postapproval inspection.

ORA and CDER review of information may overlap because applicants are being encouraged to share more product and process development information with CDER in accordance with FDA guidance.[37] The investigator should incorporate CDER insights into the inspectional evaluation of the proposed commercial process and should discuss inspectional findings regarding the adequacy of the establishment's Stage 2 process validation plans (i.e., process performance qualification plans) with OPMA. The investigator should discuss process performance qualification plan issues with the firm, document the discussion in the EIR for CDER review, and, when applicable, document pertinent observations on Form FDA 483.

OPQ requires that certain data be filed to demonstrate that aseptic filling and sterilization processes are validated before approval is granted. OPMA's review of this summary information is complemented by FDA's on-site inspection of these operations. Evaluating the adequacy of process validation at a facility is critical to ensure implementation of reproducible processes.

The investigator may find that the inspected establishment was not responsible for performing some of the process development activities and studies, and that reports for development studies are not available for inspection. The investigator should collect information about each establishment involved in process development (e.g., name, address, responsible person, work performed). This information should be included in the EIR. The OPMA manufacturing assessor will then determine if additional facilities need to be evaluated or inspected.

Related regulations for finished pharmaceuticals: 21 CFR 211.100(a) and 211.110 require developing a well-designed and reproducible process as well as appropriate change management procedures, and 21 CFR 211.22 covers the quality unit's responsibilities. Aseptic and sterilization processes are required to be validated by 21 CFR 211.113(b) and 211.42.

Related guidance for APIs: Refer to ICH Q7, sections XII.A (Validation Policy) through XII.E (Process Validation Program) for guidance regarding process validation and section XIII, Change Control for guidance regarding change management.

[37] See, e.g., ICH guidance for industry *Q8(R2) Pharmaceutical Development*. See also draft guidance for industry *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence)*. When final, this guidance will represent FDA's current thinking on this topic.

(2) Objective 2: Conformance to Application

Verify that the formulation, manufacturing, or processing methods; analytical (or examination) methods; and batch records are consistent with descriptions contained in the CMC section of the application. This may include CMC information relevant to exhibit batches, biobatches, other pivotal clinical batches, and the proposed commercial-scale process.

To address this objective, conduct the following activities:

- Observe the processing lines, unit operations—both scale and type (including aseptic or sterilization processes)—and laboratory methods and compare with the description and/or batch records submitted in the CMC section of the application (or DMF).
- Audit the detailed manufacturing records and ensure their consistency with the general description of the processing methods described in the application. Review the biobatch and other pivotal batches and compare them with the commercial-scale process. Compare actual manufacturing records (e.g., pivotal clinical lots, biobatches, exhibit batches) to the production method described in the application and contact OPMA if significant differences are observed. It is also important to ensure that batches placed on stability for expiration date (or retest date) determination are representative of the proposed marketed product.
- Verify that the biobatch, registration/exhibit, and stability batch sizes are as reported in the CMC section. For biobatches, or pivotal clinical batches, FDA might not always visit the manufacturing establishment. However, it is important to make every effort to evaluate the records associated with the batches and understand their manufacturing context.

  Inspectional coverage of analytical methods validation for tests described in the application should include methods for testing the components, in-process materials, and finished product. Compare the methods filed with the methods in use in the facility. Review the validation data and reports for each test method to ensure that there are no significant variations from the filed method and specifications.
- Inspect the actual performance of the methods during the PAI, including laboratory deviations, trends, and other indications of a lack of method reliability. Not all methods need to be covered during the PAI. Coverage should be given particularly to methods/testing that are unique to the product application under inspection, technically complicated to perform, or measure a high-risk CQA. Consultation with the IQA team may be useful in identifying such methods.
- Audit all the records associated with the sample if an inspected establishment sent samples to FDA for analysis (as described below and in Part IV of this compliance program).
- Report as soon as possible any finding that casts doubt on the authenticity of a biobatch or whether any samples from the biobatch provided to FDA may not actually be from the biobatch specified in the application (as filed in the CMC section). Records that are considered good candidates for audit include shipping records, equipment use logs, inventory records, analytical testing results, and related research/scale-up batch records.

- Examine raw data and test records and compare them with submitted data for components used in the biobatch and finished product and records associated with biobatch production. Consultation with the CDER application assessors in advance of the inspection is essential to learn which component attributes, finished product specifications, and processing methods are critical to establishing the comparability of the biobatch and proposed commercial process.
- Inspect laboratory methods and audit research and development notebooks. Review of inventory or receiving records of APIs as well as other components is a way of verifying and evaluating the context and integrity of batch information submitted in applications.
- Verify that the API manufacturer is the same as reported in the CMC section and ensure that no other records indicate a different API manufacturer or API quality from that described in the application. If the application submission is for an API manufacturer other than the primary supplier, audit the data demonstrating the comparability (e.g., impurity profiles, physical characteristics), including quality, of the new API manufacturer with the previous manufacturer.
- Verify that the establishment has implemented a risk management system that ensures hazards (e.g., cross-contamination; adulteration; hazardous impurities such as nitrosamines,[38] nitrosating agents, nitrites, nitrates, and azides) are identified, evaluated, addressed, communicated to the establishment's management and FDA, and continuously reviewed as needed throughout a product's lifecycle. Consultation with the IQA team regarding potential hazards or hazardous risk may be useful before the inspection. If impurity risks are identified, consult the IQA team as appropriate, and include coverage of one or more of the following, as needed:
    - Verify that the establishment has conducted a risk assessment for hazardous impurities and has implemented strategies and a corresponding risk management system (e.g., actions to address sources of variability, release testing, reduction or elimination of impurities, cleaning validation) to control and mitigate the risk. Ensure that this includes impurity risks identified in the application.
    - Verify that unacceptable levels of hazardous impurities are documented and risks are mitigated.
    - Verify that the establishment has a control strategy for operations identified as at risk of forming hazardous impurities.
    - Confirm that acceptable specification limits have been established for hazardous impurities if identified in components, the finished product, or as a degradant throughout the product's lifecycle.
    - Determine whether changes that may impact the type or level of impurities are appropriately evaluated within the establishment's change management system throughout the product's lifecycle.

[38] See guidance for industry *Control of Nitrosamine Impurities in Human Drugs*.

Conformance to the application under this objective may be relevant to Objective 3, Data Integrity Audit. This typically involves verification of the factual integrity of the information filed in the application and the contextual integrity of information supporting that filed information.[39]

Related regulations for finished pharmaceuticals: 21 CFR 314.50(d)(1)(ii)(b) addresses submission of biobatches, stability batch information, and finished product testing results; see related CGMP regulations at 21 CFR 211.165, 211.166, and 211.188. Component quality is addressed at 21 CFR 211.80 and 211.84; production and process control records are to be created and handled in accordance with 21 CFR 211.188; records are required to be maintained as per 21 CFR 211.180, especially (a) and (b); and methods are to be scientifically sound and validated as per 21 CFR 211.160–211.167.

Related guidance for APIs: For results of testing, batch records, and stability monitoring of APIs, refer to ICH Q7, sections XI.A, General Controls, XI.B, Testing of Intermediates and APIs, XI.E, Stability Monitoring of APIs, and VI.E, Batch Production Records. Component quality is addressed in ICH Q7, section VI.C, Records of Raw Materials, Intermediates, API Labeling and Packaging Materials; record maintenance is addressed in ICH Q7, section VI.A, Documentation System and Specifications; and the need for analytical methods to be scientifically sound and validated is discussed in ICH Q7, sections XII.H, Validation of Analytical Methods, and XI.A, General Controls.

(3) Objective 3: Data Integrity Audit

> *Audit and verify raw data at the facility that are associated with the product. This information can, among other things, help to authenticate the data submitted in the CMC section of the application as relevant, accurate, complete, and reliable for CDER assessment.*

Audit the accuracy and completeness of data reported by the facility for the product. Not every CMC data summary must be audited to accomplish this objective. The inspectional strategy may select key data sets from drug development (e.g., formulation development, Stage 1 of process validation) or randomly select data filed in the application. Generally, data on finished product stability, dissolution, content uniformity, and API impurity are good candidates for this audit.

In addition to summary tables, applicants typically submit additional testing for the finished product's performance and physicochemical attributes. During the inspection, compare raw data—hardcopy or electronic—such as chromatograms, spectrograms, laboratory analyst notebooks, and additional information from the laboratory with summary data filed in the CMC section. Raw data files should support a conclusion that the data/information reported by the site are complete and accurate. Examples of data integrity concerns include failure to scientifically justify not reporting relevant data, such as aberrant test results or absences in a submitted chromatographic sequence.

[39] Information that has factual integrity is original and corresponds directly to that submitted to FDA (e.g., a chromatogram showing a peak area that directly calculates to an assay value submitted in a data summary sheet in the application). Information that has contextual integrity supports submitted information about the testing or manufacturing area and related products/processes (e.g., a chromatographic sequence that shows all the assayed samples and that does not reveal failing assay values). Missing records (batch or testing) and unexplained losses of inventory of components used in production may call into question the contextual integrity of the information filed in an application.

When data discrepancies are observed, identify firm personnel involved. Determine which actions or inactions contributed to the data integrity problem and whether corrective actions were or are to be taken. Also determine whether data that should have been reported in the application were not reported. For example, did the firm:

- Substitute passing data (i.e., within specification or otherwise favorable) for failing data (i.e., out of specification or unfavorable) without a sufficient investigation and resolution of the discrepancy?
- Improperly invalidate out-of-specification results?

Following are possible indications of data integrity problems:

- Alteration of raw, original data and records (e.g., the use of correction fluid).
- Records, reports, or information referring to failing biostudies.
- Discrepancies (e.g., color, shape, embossing) between material used in a biostudy and reserve samples.
- Inconsistencies in manufacturing documentation (e.g., identification of actual equipment used) and other information in the submission.
- Multiple analyses of assay using the same sample without adequate justification.
- Exclusion of specific lots from the stability program to avoid submitting failed results.
- Reworking or process modifications not adequately justified or appropriately reported.
- Manipulation of a poorly defined analytical procedure and associated data analysis to obtain passing results.
- Backdating stability test results to meet required commitments.
- Fabrication of acceptable test results without performing the test.
- Use of test results from previous batches to substitute testing for another batch.
- The site does not actually manufacture the drug as described in the drug application or the DMFs referenced therein.[40]

The investigators should clearly indicate in the EIR whether their findings call into question the reliability of the submitted data. Specific data/information filed in the application should be referenced, when possible. It is essential that the ORA division notify OPMA of data reliability concerns promptly to trigger an immediate evaluation of the impact on the application. If such situations are observed, thoroughly document the unreliable data (see III.2.B, Completion of the Establishment Inspection Report).

If a pattern of data reliability issues is identified during a PAI, the investigator should consider expanding the coverage to surveillance of marketed products manufactured in the facility using compliance program 7356.002. If data reliability issues are documented for other products during an

[40] The inspection team should determine if the operations appear beyond the firm's capability and should review various production records to determine if batches were truly produced at the site or are being produced at a subcontracted shadow factory without FDA knowledge.

expanded inspection, this suggests a broader pattern that implicates all products manufactured at the facility. If so, ORA should consider submitting a recommendation that CDER consider invoking the Application Integrity Policy (AIP) or that a for-cause inspection be planned to further define the scope of the data reliability issues. Contact information and procedures for OC's Office of Manufacturing Quality (OC/OMQ) are on the AIP website.[41]

Related regulations for finished pharmaceuticals: 21 CFR 314.50(d) requires that the CMC section include "data and information in sufficient detail to permit the agency to make a knowledgeable judgment about whether to approve the application." Several CGMP regulations require laboratory data to be collected and maintained, including 21 CFR 211.160 (General Requirements), 211.165 (Testing and Release for Distribution), 211.166 (Stability Testing), and 211.167 (Special Testing Requirements).

Related guidance for APIs: Several ICH Q7 sections require laboratory data to be collected and maintained, including XI.A (General Controls) through XI.E (Stability Monitoring of APIs).

(4) Objective 4: Commitment to Quality in Pharmaceutical Development

Assess the pharmaceutical development program by evaluating the extent to which it is supported, defined, managed, and continuously assessed for its effectiveness as well as its use in supporting continual improvement of the PQS.

Assess the establishment's ability to develop and manufacture drugs of consistent quality. This includes determining whether an establishment has implemented and follows a development program that applies sound science and principles of material science, engineering, knowledge management, and quality risk management in a holistic manner.

Evaluate the pharmaceutical development program to determine the following:

- Resources are provided to perform activities related to the development of the product or process.
- Procedures, written reports, and actions of employees and management ensure comprehensive process and product understanding to the extent possible.
- Management is aware of residual risks, and an appropriate quality management system has been implemented to ensure robust manufacturing, prevent defects and errors, and enable continual improvement through the change management system.

Evaluating the product's pharmaceutical development, scale-up, and proposed implementation at commercial scale can assist in understanding the overall pharmaceutical development program.

There are four elements supportive of the firm's commitment to quality during development:

[41] See https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/application-integrity-policy and CPG Sec 120.100 *Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities,* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-120100-fraud-untrue-statements-material-facts-bribery-and-illegal-gratuities.

1. Pharmaceutical Development Program

   Review the tools, procedures, or strategies put in place by the facility as part of its overarching pharmaceutical development program and determine whether the pharmaceutical development report for the application product aligns with the development program.

2. Senior Management Commitment to Quality

   Determine whether there are adequate documents describing the roles and responsibilities of the relevant disciplines in the development process. Determine whether there is quality assurance oversight in product development, scale-up, and technology transfer, thus ensuring development processes and procedures are implementable at the commercial scale. Determine whether upper management takes an active role to ensure that product quality is achieved, such as ensuring a multidisciplinary integrated development team.

3. Multidisciplinary Integrated Development Team

   Verify that the product development team is represented by integrated, cross-functional departments of the firm's relevant pharmaceutical disciplines (e.g., process development, engineering, quality assurance), and verify that the cross-functional departments are actively involved during development, technology transfer, and commercial manufacturing of a drug.

4. Quality Risk Management in Development

   Determine whether adequate risk assessment activities are included as part of the pharmaceutical development program and whether risk assessments identify potentially high-risk formulation and manufacturing variables that could impact drug product quality. Confirm procedures are put in place to reduce or mitigate the risk. Assess the firm's use of quality risk management principles during development and verify that adequate steps are included as part of the development program that will minimize product and manufacturing defects.

The information gathered from Objective 4 coverage during a PAI is generally used for data analysis or internal trending by FDA and may assist in identification of risk factors (e.g., risks related to process, firm history, and product) for future PAI decisions. Coverage of Objective 4 helps FDA's decision-making related to the firm's effectiveness in developing new products and integrating changes within an establishment. Objective 4 also provides an opportunity for investigators to observe and document examples of mature quality practices that exceed CGMP requirements and are indicative of an advanced quality system.

Cite significant CGMP discrepancies or deficiencies that are identified with Objective 4 coverage on Form FDA 483 under Objectives 1, 2, or 3, as applicable. Failure to conform with an element described above should not be cited on Form FDA 483 unless the discrepancy or the deficiency can be linked to a CGMP violation.

Related regulations for finished pharmaceuticals: CGMP regulations as described in Objectives 1, 2, and 3 support commitment to quality for drug product pharmaceutical development systems.

Related guidance for APIs: API references as described in Objectives 1, 2, and 3 support commitment to quality for API pharmaceutical development systems.

C. Investigator Questions and Concerns During an Inspection

Following the principles of ICH Q7, Q8, Q9, Q10, Q11, and Q12,[42] FDA is implementing a more integrated approach towards preparing for and conducting inspections. CDER and ORA will collaborate to provide an efficient and effective use of inspectional resources. Each deficiency identified by the CDER inspection participant should be discussed with the lead investigator to clarify follow-up activities and responsibilities. Questions that arise during an inspection should normally be directed to the assigned OPMA manufacturing assessor and ORA PAM. Questions and concerns may, for example, relate to facility control, process control, batch release, quality assurance, manufacturing procedures, product development summaries, product attributes, or test methods. The assigned OPMA manufacturing assessors for a given application are listed in Panorama.

2. NDA/ANDA Inspection Reporting

A. Issuance of Form FDA 483

Reportable observations from the inspection will be issued to the establishment on Form FDA 483, consistent with instructions in the IOM.[43] Significant CGMP deficiencies pertaining to the products and significant instances of application nonconformances should be cited on Form FDA 483. If the inspection is a concurrent CGMP inspection and PAI, organize Form FDA 483 according to compliance program 7356.002 and the IOM.[44] The following are examples of PAI findings that can potentially impact product quality and should appear on Form FDA 483:

- PAI findings that differ from the filed CMC description of the process for the biobatch, or stability batches; the lack of an adequate or sufficiently specific proposed commercial batch record to provide for a reproducible manufacturing operation; or inadequate procedures or instructions for controlling the process or equipment intended to support commercial operation.
- PAI findings that differ from the filed CMC description of formulations, processing principles, equipment used, or discrepancies in raw material lot reconciliation (inconsistencies in firm's records for receipt, inventory, or use in production).
- Missing data or unreliable data:
  - Data/information submitted to the application that were potentially unreliable or misleading and the relevance of these data/information.
  - Unexplained or inappropriate gaps in a chromatographic or analytical sequence.
- A pattern of inappropriately disregarding test results.
- Inadequate or lack of justification for not reporting data/information.

[42] See VI.1.D, References, for these ICH guidances for industry.

[43] See https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual.

[44] The investigator should indicate in the EIR which of the four objectives in Part III.1 of this compliance program pertain to each observation.

- Insufficiency, discrepancy, or failure of an analytical method validation program.
- Lack of suitability of the facility, equipment, or manufacturing operations—which may result from inadequate development, scale-up, or technology transfer activities—intended for making the commercial API or finished product to the CGMP regulations.
- Other specific nonconformance (e.g., conditions, practices, and procedures, including inadequate knowledge sharing and ineffective or nonexistent CAPAs) to the CGMP regulations.

B. Completion of the Establishment Inspection Report

The inspection team prepares a narrative EIR per instructions in the IOM (Chapter 5). The EIR should be completed as follows:

- Organize the EIR's Manufacturing/Design Operations section by the PAI objectives (as described in Part II of this compliance program).
- Briefly describe the responsibilities of the inspected firm in relation to the assigned application.
- Describe the manufacturing operations and summarize coverage provided during the inspection as described in this compliance program.
- Address application-related inspectional concerns communicated by the IQA team with specific data, areas covered, citations, and discussion with management.

If the inspection is a concurrent CGMP inspection and PAI, the EIR should be organized according to compliance program 7356.002.

3. Sample Collection or Sample Submission Requests

Investigators should not collect samples during the PAI unless requested as a part of the inspection assignment by CDER or on a for-cause basis. Investigators may collect samples only after getting approval from their ORA PAM or supervisor and notifying OPMA and the relevant IQA team assessor. OPMA checks with other program coordinators to verify that samples have not already been collected and can be analyzed.

OPQ/OTR/DPA as well as ORA laboratories perform testing on samples collected for method verification[45] or profiling. If an official sample is collected at an establishment, the investigator should use the appropriate PACs for method verification or profile analyses. Method verification samples are used to verify NDA/ANDA methods in FDA laboratories. Profile samples—formerly called *forensic* or *fingerprinting* samples—are used to support the integrity of the bioequivalence study, authenticating the generic product and the innovator product and providing a reference for postmarketing surveillance samples. They are typically reserve samples collected at the manufacturing site.

[45] Method verification samples are collected at the manufacturing establishment on a for-cause basis and are independent of the method verification samples that may or may not have been requested directly from the ANDA/NDA applicants under the Method Verification Program, which is managed by OPQ/OTR/DPA.

For samples at API facilities, investigators should only collect samples upon specific request by OMPTO. This process is described in Part IV of compliance program 7356.002F—*Active Pharmaceutical Ingredient (API) Process Inspection*.

For samples from non-U.S. locations, investigators should send a request for their collection to OMPTO for coordination with scheduling of the inspection. Sample collection of APIs from non-U.S. locations is described in compliance program 7356.002F, Part IV. Samples shipped to the United States are to be accompanied by the U.S. Customs Letter in Attachment C.

For permit information regarding samples derived from animal-sourced material, refer to IOM Chapter 3.2.1.6. For the collection of narcotic and controlled prescription drugs, refer to IOM Chapter 4.2.5.3.

PART IV—ANALYTICAL

For NDAs and ANDAs pending a regulatory decision, drug product samples and test methods can be collected to:

- Verify whether the firm's test methods are suitable for regulatory use and whether the drug product meets compendial or the firm's specifications.
- Verify the integrity of the bioequivalence study.
- Authenticate the proposed drug product (e.g., new, generic).
- Provide a reference standard for postmarketing surveillance.

Attachment D provides an example of sample collection instructions for solid oral dosage finished product manufacturers.

OPQ/OTR/DPA as well as ORA laboratories perform testing on samples collected. The analyzing laboratory (OPQ/OTR/DPA or ORA/ORS) maintains completed analytical worksheets. OPQ/OTR/DPA enters the laboratory results for method verification samples[46] for an NDA or ANDA into Panorama. The analyzing laboratory forwards a copy of the laboratory results to the CDER or ORA office that requested or collected samples.

The analyzing laboratory reports adverse findings by emailing a copy of the worksheet to the following recipients:

- The ORA program division for the manufacturing facility, if applicable.
- Drug substance assessor or drug product assessor assigned to the submission.

If warranted, ORA division offices may recommend an appropriate regulatory action to CDER.

[46] See footnote 45.

PART V—REGULATORY/ADMINISTRATIVE STRATEGY

1. ORA Recommendations

ORA divisions either inspect the establishment named in an application or they perform a file review and provide a recommendation for the facility's acceptability. Based on the outcome of the PAI, the ORA PAM uses Panorama to make an **approve** or a **withhold** recommendation.

A. Approve Recommendation

The ORA PAM makes an **approve** recommendation if there are no significant issues that would adversely impact the establishment's ability to perform its designated functions described in the application.

B. Withhold Recommendation

The ORA PAM makes a **withhold** recommendation if there are significant issues that would adversely impact the establishment's ability to perform its designated functions described in the application. For example:

1. Significant data integrity problems, including misrepresented data or other conditions related to the submission batches.
2. Serious CGMP concerns with the manufacture of a biobatch or pivotal clinical, exhibit, or validation batches such as changes to formulation or processing.
3. Significant differences between the process used for pivotal clinical batches or biobatches and application exhibit batches.
4. Lack of complete manufacturing and control instructions in the master production record or lack of data to support those instructions.
5. Lack of capacity to manufacture the drug product or API. (If the firm is not ready for an inspection, the division should request a letter from the establishment.)
6. Failure to meet application commitments (e.g., the firm is not performing functions as listed or described in the application).
7. Full-scale process performance qualification studies attempted and failed before the PAI, which demonstrate that the process is not under control and the establishment is not making appropriate changes.
8. For products for which full-scale summary information is provided in the application, no demonstration that the product (1) can be reliably manufactured at commercial scale or (2) can meet its CQAs.
9. Incomplete or unsuccessful analytical method validation or verification.
10. No clear identification of equipment or processing parameters in records for biobatches, pivotal clinical batches, or exhibit batches.

11. Significant failures related to the stability study, which raise questions about the stability of the product or API.
12. Failure to report adverse findings or failing test data without appropriate justification.
13. Delaying, denying, limiting, or refusing a drug inspection.[47]

2. Additional Considerations

If the ORA division recommends **withhold** for an application because of deficiencies and findings for inspectional coverage under compliance program 7356.002, the division enters a pOAI alert in Panorama and considers recommending an advisory or enforcement action. The Office of Compliance reviews ORA's recommendation for appropriate action if necessary, including when significant CGMP findings are identified that may affect marketed product.

OPMA reviews the PAI results (EIRs, Form FDA 483s, firm responses, ORA division evaluation of the firm responses) when ORA divisions recommend **withhold** and provides a recommendation in Panorama. OPMA updates the final decision and profiles (as appropriate) in eNSpect and shares the review of the EIR, facility recommendation, and impact on the regulatory action with the IQA team. In addition, OPMA will update the Compliance Management System (CMS) with information pertinent to the review.

Should additional information (e.g., firm response or its evaluation by the ORA division) become available within a reasonable time frame before the OPQ application action date, OPMA may update its assessment and facility recommendation. Alternatively, OPMA may defer further assessment to the next assessment cycle for the subject application. An OPMA decision to recommend facility approval depends on satisfactory correction of the findings that led to the initial **withhold** recommendation. OPMA and ORA may confirm satisfactory corrective action using a follow-up inspection.

When the ORA division recommends **withhold** for a PAI of an establishment that does not market FDA-regulated products, a warning letter is not usually the appropriate regulatory action. However, if objectionable findings are observed and the findings affect marketed drugs, refer to the drug manufacturing inspection compliance program 7356.002.

Exception to withhold recommendation: ORA divisions will not recommend withholding approval of NDAs and ANDAs solely for a lack of complete commercial-scale process validation at the time of a PAI (see also guidance for industry *Process Validation: General Principles and Practices* and CPG Sec. 490.100 *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*[48]). Although sufficient process validation studies may not have been completed at the time of the PAI to release the product, the firm must achieve a high degree of assurance that the manufacturing process consistently produces a product that meets its quality attributes before distribution.

[47] See guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*.

[48] See https://www.fda.gov/media/71756/download.

PART VI—REFERENCES, ATTACHMENTS, PROGRAM CONTACTS, AND ACRONYMS

1. References

A. Code of Federal Regulations, Title 21

https://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

Parts 210 and 211: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs and Current Good Manufacturing Practice for Finished Pharmaceuticals

Part 310: New Drugs

Part 314: Applications for FDA Approval To Market a New Drug

B. Compliance Programs

(1) Bioresearch Monitoring

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-guidance-manual-cpgm/bioresearch-monitoring-program-bimo-compliance-programs

7348.003—*In Vivo Bioavailability/Bioequivalence Studies (Clinical)*

7348.004—*In Vivo Bioavailability/Bioequivalence Studies (Analytical)*

(2) Drugs

https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs

7353.001—*Postmarketing Adverse Drug Experience (PADE) Reporting Inspections*

7356.002—*Drug Manufacturing Inspections*

7356.002A—*Sterile Drug Process Inspections*

7356.002F—*Active Pharmaceutical Ingredient (API) Process Inspection*

7356.002P—*Positron Emission Tomography (PET) CGMP Drug Process and Pre-Approval Inspections/Investigations*

C. Compliance Policy Guides

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/manual-compliance-policy-guides

CPG Sec. 490.100 *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*

CPG Sec. 490.200 *Parametric Release of Parenteral Drug Products Terminally Sterilized by Moist Heat*

D. Guidances

https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

(1) Guidances for Industry

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997)

Changes to an Approved NDA or ANDA (April 2004)

Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection (October 2014)

CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports (March 2014)

Control of Nitrosamine Impurities in Human Drugs (February 2021)

PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (September 2004)

Process Validation: General Principles and Practices (January 2011)

Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency (April 2021)

Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (November 1994)

Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes (February 2010)

*Also see FDA's Scale-Up and Postapproval Changes (SUPAC) guidances for industry.

(2) Draft Guidances for Industry[49]

ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications (Pre-Submission Facility Correspondence) (November 2017)

Conducting Remote Regulatory Assessments: Questions and Answers (July 2022)

ICH Q12: Implementation Considerations for FDA-Regulated Products (May 2021)

(3) ICH Guidances for Industry

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016)

Q8(R2) Pharmaceutical Development (November 2009)

Q9 Quality Risk Management (June 2006)

Q10 Pharmaceutical Quality System (April 2009)

Q11 Development and Manufacture of Drug Substances (November 2012)

[49] When final, these guidances will represent FDA's current thinking on these topics.

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management and its Annexes (May 2021)

E. FDA Procedures and References

Guides to Inspection, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-guides

- *Pharmaceutical Quality Control Laboratories*
- *Microbiological Pharmaceutical Quality Control Laboratories*
- *Validation of Cleaning Processes*
- *Lyophilization of Parenterals*
- *High Purity Water Systems*
- *Foreign Pharmaceutical Manufacturers*

Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations (June 2017), https://www.fda.gov/drugs/pharmaceutical-quality-resources/integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept-operations

Investigations Operations Manual (2021), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual

MAPP 5014.1 *Understanding CDER's Risk-Based Site Selection Model* (September 2018), https://www.fda.gov/media/116004/download

Pharmaceutical Quality for the 21st Century—A Risk-Based Approach: Progress Report (May 2007), https://www.fda.gov/about-fda/center-drug-evaluation-and-research/pharmaceutical-quality-21st-century-risk-based-approach-progress-report

Staff Manual Guide 9004.1, *Policy and Procedures for Requesting Records in Advance of or in Lieu of a Drug Inspection* (August 2017), https://www.fda.gov/media/124338/download

An Update to the Resiliency Roadmap for FDA Inspectional Oversight (November 2021), https://www.fda.gov/media/154293/download

F. FDA User Fee Programs

https://www.fda.gov/industry/fda-user-fee-programs

Prescription Drug User Fee Act (PDUFA)

Generic Drug User Fee Amendments (GDUFA)

2. **Attachments**

Attachment A: Remote Regulatory Assessments

Attachment B: CDER-ORA Collaboration for Ensuring Product Quality

Attachment C: Example of U.S. Customs Letter

Attachment D: Example of Sample Collection Instructions for Solid Oral Dosage Finished Product Manufacturers

3. Program Contacts

A. Center for Drug Evaluation and Research

CGMP or Quality-Related Policy Questions
For CGMP or quality-related policy, technical, or scientific questions or information needs, including questions about this compliance program, send an email to the following address and it will be handled as a top priority:
OPQPolicy@fda.hhs.gov

Office of Compliance: Enforcement-Related Guidance or Policy
For enforcement-related guidance or policy, including evidence need and sufficiency, citations, and case evaluation/recommendation advice related to marketed products or surveillance coverage, send an email to the following address and it will be handled as a top priority:
CDEROMQCompliance@fda.hhs.gov

Laboratories
Division of Pharmaceutical Analysis
645 South Newstead Avenue
St. Louis, MO 63110

Drug Applications
Submission information for NDAs and ANDAs (general):

- Forms & Submission Requirements web page: https://www.fda.gov/drugs/development-approval-process-drugs/forms-submission-requirements
- Guidance Documents for Drug Applications web page: https://www.fda.gov/drugs/development-approval-process-drugs/guidance-documents-drug-applications

Questions about NDA and ANDA content:

- Refer to application contacts in Panorama

Bioequivalence Study Issues
Office of Compliance, Office of Scientific Investigations
https://www.fda.gov/about-fda/center-drug-evaluation-and-research/office-scientific-investigations

B. Office of Regulatory Affairs

Office of Medical Products and Tobacco Operations
Office of Pharmaceutical Quality Operations, Division of Pharmaceutical Quality Programs, Pharmaceutical Quality Initiatives Branch
ORA program coordinators: See the ORA Directory in the IOM for updated references, https://www.fda.gov/files/inspections,%20compliance,%20enforcement,%20and%20criminal%20investigations/published/ORA--Directory.pdf

Office of Regulatory Science
Office of Medical Products, Tobacco, and Specialty Laboratory Operations
Deputy Associate Director
ORSOMPSLOProgramCoordinators@fda.hhs.gov
https://www.fda.gov/science-research/field-science-and-laboratories/about-office-regulatory-science-ors

4. Acronyms

ADE:	adverse drug experience
AIP:	Application Integrity Policy
ANDA:	abbreviated new drug application
API:	active pharmaceutical ingredient
CAPA:	corrective action and preventive action
CDER:	Center for Drug Evaluation and Research
CGMP:	current good manufacturing practice
CMC:	chemistry, manufacturing, and controls
CMS:	Compliance Management System
CQA:	critical quality attribute
DFR:	district file review
DMF:	drug master file
EC:	established condition
EIR:	establishment inspection report
FAR:	field alert report
FD&C Act:	Federal Food, Drug, and Cosmetic Act
GDUFA	Generic Drug User Fee Amendments
ICH:	International Council for Harmonisation
IOM:	Investigations Operations Manual
IND:	investigational new drug
IQA:	integrated quality assessment
MRA:	mutual recognition agreement
NDA:	new drug application
OAI:	Official Action Indicated
OC:	Office of Compliance
OMPTO:	Office of Medical Products and Tobacco Operations
OMQ:	Office of Manufacturing Quality
OPMA:	Office of Pharmaceutical Manufacturing Assessment
OPQ:	Office of Pharmaceutical Quality
OPQ/ OTR/DPA:	Division of Pharmaceutical Analysis in OPQ's Office of Testing and Research
ORA:	Office of Regulatory Affairs
ORS:	Office of Regulatory Science
PAC:	product/assignment code
PAI:	preapproval inspection
PAM:	preapproval program manager
PDUFA:	Prescription Drug User Fee Act
PET:	positron emission tomography
PLCM:	product lifecycle management
PLI:	prelicense inspection
pOAI:	potential Official Action Indicated
PQS:	pharmaceutical quality system

RRA: remote regulatory assessments

RIE: remote interactive evaluation

PART VII—CENTER AND ORA RESPONSIBILITIES

CDER and ORA recently redefined their roles and responsibilities regarding application assessments and inspections of human drugs facilities under the ConOps *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*. This ConOps operating model applies to pre- and postapproval, surveillance, and for-cause inspections. The new roles and responsibilities for PAIs, as explained in ConOps, are being implemented and described in the compliance program, including the activities described in Attachment B.

ATTACHMENT A: REMOTE REGULATORY ASSESSMENTS

In addition to its inspectional authority, FDA may conduct remote regulatory assessments (RRAs), under certain circumstances, to support oversight of FDA-regulated products and establishments.[1] An RRA is an examination of an FDA-regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements. RRAs assist in protecting human health, informing regulatory decisions, and verifying certain information submitted to the Agency.

RRAs used in lieu of or in advance of inspections have allowed FDA to remotely evaluate drug manufacturing establishments to mitigate risks. However, RRAs are not the same as an inspection as described in section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and FDA does not consider them to satisfy the statutory requirement for an inspection under section 510(h) of the FD&C Act.

The following RRAs, along with applicable FDA policies, can be used to support the objectives of this compliance program when, in the opinion of FDA experts, they would enable FDA to determine whether the establishment meets applicable requirements for the product's identity, strength, quality, and purity for an application subject to section 505 of the FD&C Act.

1. FDA Records and Other Information Requests Under Section 704(a)(4) of the FD&C Act (Statutorily Authorized RRA)

In 2012, with the passage of the Food and Drug Administration Safety and Innovation Act to amend the FD&C Act, Congress gave FDA the authority to request "any records or other information" in advance of or in lieu of an inspection related to human or animal drugs, including human biological drug products. Section 704(a)(4) of the FD&C Act requires "a person that owns or operates an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug" to provide FDA, upon request, records or other information that FDA may inspect under section 704(a)(1).

With regards to this compliance program, a 704(a)(4) request may be used in lieu of or in advance of a preapproval inspection (PAI) to support assessment of a pending application or supplement.[2] The use of 704(a)(4) authority does not prevent an FDA investigator from requesting records or other information on inspection.

[1] See FDA's *An Update to the Resiliency Roadmap for FDA Inspectional Oversight*, section 704 of the Federal Food, Drug, and Cosmetic Act, and draft guidance for industry *Conducting Remote Regulatory Assessments: Questions and Answers* (July 2022). When final, this guidance will represent FDA's current thinking on this topic.

[2] Staff Manual Guide 9004.1, *Policy and Procedures for Requesting Records in Advance of or in Lieu of a Drug Inspection*.

2. Remote Interactive Evaluation (Voluntary RRA)

A remote interactive evaluation (RIE) is an evaluation of a firm's compliance with regulations and/or conformance with an application submission that a firm participates in voluntarily.[3] RIEs are defined as FDA's use of any combination of remote interactive tools (e.g., remote livestreaming video of operations, teleconferences, screen sharing) to evaluate facilities where drugs are manufactured, processed, packaged, or held. FDA may request to conduct an RIE whenever a program office determines it is appropriate based on mission needs.

With regards to this compliance program, an RIE may be used in lieu of or in advance of a PAI to support assessment of a pending application or supplement. During an inspection, FDA may collect copies of previously received documents and other documents not previously requested.

[3] See guidance for industry *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergenc*y.

ATTACHMENT B: CDER-ORA COLLABORATION FOR ENSURING PRODUCT QUALITY

In the ConOps framework, preapproval inspections (PAIs) are integrated with application assessments to help identify and resolve product quality issues.[1] This integrated approach generally involves the following activities:

- **IQA team assessment before the PAI,** during which the integrated quality assessment (IQA) team assesses the application risks to product quality that could impact safety and efficacy, including bioequivalence, and recommends whether a PAI is needed. If a PAI is needed, the IQA team communicates risks and concerns regarding the quality of the product, process, and facility to the inspection team.
- **PAI,** during which the inspection team performs the on-site inspection for the specified application(s) in accordance with the objectives of this compliance program and current good manufacturing practice (CGMP), discusses inspection findings, and, if warranted, lists significant deficiencies on Form FDA 483, which is issued to the inspected facility.

  The facility provides responses to the issued Form FDA 483, including proposed corrective and preventive actions, if required, to the Office of Regulatory Affairs (ORA).
- **IQA team assessment after the PAI,** during which:
  - ORA provides the IQA team with the firm's responses, including the proposed corrective and preventive actions and its initial facility recommendation.
  - The IQA team assesses the inspection findings (e.g., inspection team's recommendation, establishment inspection report, Form FDA 483, firm responses) and consults inspection team members as needed.
  - The IQA team addresses outstanding product quality issues impacting application approval, and the Center for Drug Evaluation and Research (CDER) communicates with the applicant, drug master file (DMF) holder, or inspected facility (e.g., if the facility owner differs from the applicant), as appropriate.
  - The Office of Pharmaceutical Manufacturing Assessment (OPMA), in CDER's Office of Pharmaceutical Quality (OPQ), makes the final facility recommendation to the IQA team.
  - The IQA team makes the quality recommendation for the application.

The table below highlights some quality-related topics with specific examples of how quality risks could be addressed through integration of application assessments and PAIs. As depicted in the table, FDA communications about quality issues vary because, depending on the facility inspected and the specific quality topic, the responsibility for resolving FDA concerns resides with either the applicant or the inspected facility. In general, FDA expects that the facility will resolve deficiencies identified on Form FDA 483 as they relate to ensuring compliance with CGMP, and the applicant will resolve any relevant application deficiencies resulting from inspection coverage.

[1] See *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*, https://www.fda.gov/drugs/pharmaceutical-quality-resources/integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept-operations.

Addressing Quality-Related Topics via an Integrated Approach			
Quality Topic	**Integrated Approach**		
	IQA Team Assessment Before PAI	**PAI**	**IQA Team Assessment After PAI**
API* manufacturing and control (e.g., production of intermediates, micronization)	The IQA team assesses CMC and associated Type II DMF information pertaining to the API and/or relevant intermediates as well as other information about the subject facility. The IQA team identifies and documents risks and concerns pertaining to the quality of the API and/or intermediates.	The inspection team evaluates the facility for conformance with ICH Q7, compliance program 7356.002F, the application, and the associated DMF and evaluates the on-site mitigation strategy and controls for the risks and concerns identified by the IQA team.	ORA provides the IQA team with its initial facility recommendation. The IQA team assesses the inspection findings, responses, and their impact on application approval. CDER, on behalf of the IQA team, may communicate with the applicant, DMF holder, or inspected facility (e.g., if the facility owner differs from the applicant), as appropriate, to resolve outstanding quality issues.
	For example: The IQA team recommends a PAI of an API/intermediate facility and communicates the API/intermediate risks and concerns to the inspection team. →	The inspection team finds that raw data generated at the API facility are unreliable and includes on Form FDA 483 its observations about missing or omitted data, overwriting of data, testing into compliance, and other deficiencies as described in Objective 3 of this compliance program. →	The IQA team works with the inspection team to understand the impact on the application (and/or DMF). The IQA team determines if additional data and studies are needed to support the application.

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Addressing Quality-Related Topics via an Integrated Approach

Quality Topic	Integrated Approach		
	IQA Team Assessment Before PAI →	**PAI** →	**IQA Team Assessment After PAI**
Novel excipient manufacturing (e.g., novel manufacturing method, noncompendial excipients (used in specialized dosage forms and special delivery systems))	The IQA team works with other disciplines, as appropriate, to assess information relevant to novel excipients and determines the risks and concerns pertaining to the quality of the novel excipient. Novel excipient manufacturers are not routinely inspected, unless specifically requested by the IQA team.	The inspection team evaluates the excipient facility for conformance with CGMP, such as the adequacy of the supplier's qualifications, ongoing QC testing regimen, and storage/handling practices and procedures. The inspection team evaluates the on-site mitigation strategy and controls for the risks and concerns identified by the IQA team.	ORA provides the IQA team with its initial facility recommendation. The IQA team assesses the inspection findings and their impact on application approval. CDER, on behalf of the IQA team, may communicate with the applicant, DMF holder, or inspected facility, as appropriate, to resolve outstanding quality issues. The IQA team, which may consult with other CDER staff, may use findings of substandard excipients to request that the applicant update the application, for example, with revised excipient specifications. Application approval by CDER includes appropriate controls for excipient quality.
	For example: The IQA team recommends a PAI of the excipient manufacturing facility to better assess identified excipient risks and communicates the risks and concerns to the inspection team. →	The inspection team finds that released excipient lots do not meet the excipient manufacturer's specifications and includes its observations on Form FDA 483. →	The IQA team communicates excipient quality concerns with the inspected facility and applicant and requests that the applicant update the application with revised excipient specifications.

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Addressing Quality-Related Topics via an Integrated Approach

Quality Topic	Integrated Approach		
	IQA Team Assessment Before PAI →	**PAI** →	**IQA Team Assessment After PAI**
Manufacturing and control of finished product • Control of raw materials and components	The IQA team may communicate to the inspection team specific risks or concerns about the quality of raw materials and components (e.g., APIs, excipients) with characteristics controlling or contributing to drug product CQAs. The IQA team reviews raw material controls, such as specifications for adequacy and appropriateness.	The inspection team evaluates the adequacy of the supplier's qualifications, ongoing QC testing, laboratory controls, storage/handling, and sampling procedures in accordance with CGMP.	ORA provides the IQA team with its initial facility recommendation. The IQA team assesses the inspection findings and their impact on component quality to make the quality recommendation. CDER, on behalf of the IQA team, may communicate with and request that the applicant, component's DMF holder, or inspected facility make appropriate changes to resolve outstanding issues with the quality of components. Application approval by CDER includes appropriate raw material controls.
	For example: The IQA team identifies a risk associated with a component critical to drug product CQAs and asks the inspection team to verify component quality and evaluate the supplier qualification program at the facility. →	The inspection team finds that the specifications in the supplier's COA and in the application do not match (e.g., supplier specifications are wider than indicated in the application), the component supplier's COA is not periodically verified, and the supplier is not reliable. The inspection team includes its observations on Form FDA 483. →	The IQA team assesses the supplier's COA collected on inspection, determines acceptability of component quality, and communicates with the applicant/facility owner. The applicant updates the component specification in the application.

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Addressing Quality-Related Topics via an Integrated Approach			
Quality Topic	**Integrated Approach**		
	IQA Team Assessment Before PAI →	**PAI** →	**IQA Team Assessment After PAI**
Manufacturing and control of finished product • Finished product test methods and acceptance criteria	The IQA team assesses test methods and acceptance criteria for the finished drug product submitted in the application.	The inspection team evaluates the integrity of test data submitted in the application and reports questionable data to the IQA team. The inspection team assesses whether the test method has been verified to operate under specified conditions of use.	ORA provides the IQA team with its initial facility recommendation. The IQA team assesses the inspection findings to make the quality recommendation. Application approval by CDER includes approval of the drug product control strategy, including finished product testing and acceptance criteria.
	For example: The IQA team communicates to the inspection team specific risks and concerns regarding test methods (e.g., suitability and validation data) and acceptance criteria (e.g., adequacy and verification of submitted data). →	The inspection team finds dissolution data that were not submitted to the application and includes its observations on Form FDA 483. →	The IQA team, which is responsible for recommending approval of the dissolution specification, uses the findings about the additional data to request that the applicant update the application with a revised dissolution specification.

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Addressing Quality-Related Topics via an Integrated Approach			
Quality Topic	**Integrated Approach**		
	IQA Team Assessment Before PAI →	**PAI** →	**IQA Team Assessment After PAI**
Manufacturing and control of finished product • Comparison of pilot-scale batches and proposed commercial-scale batches	The IQA team assesses the process design's overall development, including a review of manufactured batches (e.g., biobatch; pilot-scale, exhibit, or commercial-scale batch), proposed commercial manufacturing information, and available test data. The IQA team also determines if differences between pilot- and commercial-scale batch processes could adversely impact product quality. The IQA team communicates to the inspection team risks and concerns relevant to product/process development and commercial scale-up challenges. Product/process development facilities are not routinely inspected, unless specifically requested by the IQA team.	The inspection team evaluates the facility for conformance with CGMP, the objectives of this compliance program, and the risks and concerns identified by the IQA team. The inspection team compares the firm's development and scale-up studies (e.g., scale-up from the biobatch, or pivotal batches, to a larger interim or full-scale batch) with the proposed commercial process and reports significant manufacturing process changes (including control strategy) and differences in equipment operating principles.	ORA provides the IQA team with its initial facility recommendation. The IQA team assesses the inspection findings and their impact on the drug product control strategy to make the quality recommendation. If the inspection findings indicate differences between pilot-scale and proposed commercial-scale manufacturing that could adversely impact product quality, CDER, on behalf of the IQA team, may communicate with the applicant or inspected facility, as appropriate. The IQA team may request that the applicant perform additional studies to support the application and the proposed control strategy at the commercial site.
	For example: The IQA team requests inspection of any facility involved in the development of the drug product, including exhibit batches, if it differs from the commercial facility. →	The inspection team finds that exhibit batches were not manufactured under CGMP or as indicated in the application, which raises a concern about product quality. The inspection team includes its observations on Form FDA 483. →	The IQA team uses the finding of differences between pilot- and commercial-scale batch manufacturing methods to request that the applicant update the application with study data to ensure drug quality for the commercial-scale batches.

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Addressing Quality-Related Topics via an Integrated Approach

Quality Topic	Integrated Approach		
	IQA Team Assessment Before PAI →	**PAI** →	**IQA Team Assessment After PAI**
Manufacturing and control of finished product • Parametric release (for terminally sterilized drug products)	The IQA team assesses the overall drug product control strategy, including parametric release, included in the application (e.g., proposed terminal sterilization cycle, critical process parameters, acceptance criteria that will allow critical process controls to act as surrogates for sterility testing).**	The inspection team evaluates the facility for conformance with CGMP (e.g., preventative maintenance program, facility, equipment, quality system (investigations and batch release)), the objectives of this compliance program and compliance program 7356.002A, and the risks and concerns identified by the IQA team regarding the parametric release control strategy.	ORA provides the IQA team with its initial facility recommendation. The IQA team assesses the inspection findings and their impact on the parametric release control strategy to make the quality recommendation. If the inspection findings include quality issues related to validation data, CDER, on behalf of the IQA team, may communicate with the applicant or inspected facility, as appropriate. Application approval by CDER includes approval of the parametric release control strategy (e.g., the critical process parameters that will be used as a surrogate for sterility testing).
	For example: The IQA team identifies the risks and concerns regarding the proposed parametric release control strategy and communicates them to the inspection team. →	The inspection team finds that during validation of the terminal sterilization process, the autoclave load patterns (a critical control) are not as described in the application and that the firm did not adhere to the quality unit-approved parametric release protocol. The inspection team includes its observations on Form FDA 483. →	The IQA team uses the inspection findings to request that the applicant update the application (e.g., with additional validation study data and/or a revised parametric release control strategy).

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Addressing Quality-Related Topics via an Integrated Approach			
Quality Topic	**Integrated Approach**		
	IQA Team Assessment Before PAI →	**PAI** →	**IQA Team Assessment After PAI**
Manufacturing and control of finished product • Sterility assurance (for sterile drug products)	The IQA team assesses the sterility control and assurance information provided in the application (e.g., suitability of the selected methods of sterilization, adequacy of critical process parameters, test method selection, specifications).	The inspection team evaluates the facility regarding sterility assurance, conformance with CGMP, and the objectives of this compliance program and compliance program 7356.002A. For example, the inspection team evaluates the state of control of the process as well as the manufacturing procedures, practices, and controls employed to ensure product sterility. The inspection team also evaluates the risks and concerns identified by the IQA team.	ORA provides the IQA team with its initial facility recommendation. The IQA team assesses the inspection findings and their impact on sterility assurance to make the quality recommendation. If the inspection findings are about the aseptic process, CDER, on behalf of the IQA team, may communicate with the applicant or inspected facility, as appropriate. Application approval by CDER includes approval of the sterility assurance control strategy.
	For example: The IQA team identifies risks and concerns regarding the sterilization process and controls for sterility assurance (e.g., environmental monitoring program, media-fill, process validation) and communicates them to the inspection team. →	The inspection team finds that the aseptic processing area is deficient regarding the environmental monitoring program and includes its observations on Form FDA 483. →	The IQA team uses the inspection findings to request that the facility update its environmental monitoring program to address the risks to sterility assurance of the product.

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Addressing Quality-Related Topics via an Integrated Approach			
Quality Topic	**Integrated Approach**		
	IQA Team Assessment Before PAI →	**PAI** →	**IQA Team Assessment After PAI**
Manufacturing and control of finished product • Established conditions • Proposed changes to established conditions	The IQA team assesses the application to determine whether ECs and reporting categories for changes in ECs are identified. If coverage of development studies supporting ECs is needed, or if coverage of the PQS is needed to address risks related to potential EC changes or FDA's knowledge of the firm's PQS, the IQA team conveys its concerns to the inspection team.	When applicable, the inspection team ensures the facility has adequate development data and other information to support the proposed ECs and the firm has an adequate change management system/PQS to manage the proposed ECs.	The IQA team may request that the applicant perform additional studies to support the application and the proposed control strategy at the commercial site. The IQA team may also request that the applicant modify the EC or the reporting category when there are concerns about the firm's PQS.
	For example: The firm identifies blender revolutions as an EC and proposes a lower reporting category (e.g., annual report) based on supporting data in the application. The IQA team recommends that the inspection team look into procedures in place associated with assessing impact on product quality with changes to blender revolution. →	The inspection team finds that the change management system is deficient and includes its observations on Form FDA 483. →	The IQA team works with the inspection team to understand the impact on the application; communicates quality concerns with the applicant and requests that they update the application to reflect a higher reporting category (e.g., consistent with recommendations in guidance); and communicates quality concerns with the inspected facility.

[*] Acronyms used throughout table: API=active pharmaceutical ingredient; CDER=Center for Drug Evaluation and Research; CGMP=current good manufacturing practice; CMC=chemistry, manufacturing, and controls; COA=certificate of analysis; CQA=critical quality attribute; DMF=drug master file; EC=established condition; ICH Q7=International Council for Harmonisation guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*; IQA=integrated quality assessment; ORA=Office of Regulatory Affairs; PAI=preapproval inspection; PQS=pharmaceutical quality system; QC=quality control.

[**] For further information, see CPG Sec. 490.200 *Parametric Release of Parenteral Drug Products Terminally Sterilized by Moist Heat*, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-490200-parametric-release-parenteral-drug-products-terminally-sterilized-moist-heat.

ATTACHMENT C: EXAMPLE OF U.S. CUSTOMS LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Office of Medical Products and Tobacco Operations
Address:
Telephone:
Fax:

Date:

U.S. Customs Inspector:

The U.S. Food and Drug Administration (FDA) has requested samples of [Product] from [Company Name] for analysis by [Designated Laboratory]. We are testing the product in connection with a [an abbreviated] new drug application that has been filed with FDA.

For this reason, we are requesting that the U.S. Customs Inspector refrain from opening the immediate container. If for some reason the immediate container must be opened, please contact my office so that the sample can be opened in the presence of an FDA representative.

If there are questions regarding this request, please contact me by telephone at [Telephone Number] or by fax [Fax Number].

Sincerely,

Director/Preapproval Coordinator, Office of Medical Products and Tobacco Operations

ATTACHMENT D: EXAMPLE OF SAMPLE COLLECTION INSTRUCTIONS FOR SOLID ORAL DOSAGE FINISHED PRODUCT MANUFACTURERS

The following checklist is for the collection of samples and their submission to the Division of Pharmaceutical Analysis in the Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research.

1. Assemble and provide the following:
    a. Finished product: 20 units.
    b. Active pharmaceutical ingredients (APIs): 2–5 grams.
    c. Excipients: 2 grams (e.g., lactose, starch, microcrystalline cellulose).
    d. Manufacturing instructions for the lot collected (the batch record for the biobatch).
    e. Certificates of analysis for APIs and excipients.
        i. Use of plastic spatulas is recommended. Submit an unused plastic spatula with the sample.
        ii. Use necessary precautions to protect the samples from contamination by human hands, dust, etc. Only opaque, nonreactive, small plastic, or glass containers are appropriate as sample containers. Plastic bags are not recommended because of leakage. Care should be taken when shipping amber glass bottles to ensure breakage will not occur.
        iii. Each container should be labeled with the name of the ingredient, expiry date, lot number, complete name of your establishment, and application number and name of the product.
        iv. For an international establishment shipping the sample through U.S. Customs, a U.S. Customs Letter should accompany the sample. Refer to Attachment C.
2. Provide a material safety data sheet for each ingredient, especially for hazardous substances.
3. Provide a copy of the batch record for the biobatch, a flowchart, and a brief description of the manufacturing process. Also include the impurity test methods and impurity limits for each API. Per FDA requirements, this information will be kept confidential.
4. Include the complete firm/company name, contact information (telephone and fax numbers, email), and contact person’s name at the manufacturing establishment.

Please indicate on the shipping documents that the sample is intended for laboratory testing and has no commercial value.