

CHAPTER 56—DRUG QUALITY ASSURANCE

SUBJECT: Postapproval Inspections		IMPLEMENTATION DATE: 03/13/2023
DATA REPORTING		
PRODUCT CODES	PRODUCT/ASSIGNMENT CODE (PAC)	
Human Drugs Industry Codes: 50, 54–56, 59, 60–66.	PAC	Subject
	56843	Post-approval Inspections
	56R927	Remote Interactive Evaluation (RIE) Activities—Human Drugs
	56R928	704a4 Activities—Human Drugs
Remarks:		
<ol style="list-style-type: none"> 1. ORA should use this compliance program for postapproval inspections of manufacturing facilities in support of approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs).¹ 2. For reporting biological postapproval inspections, use the PAC 56843 under this compliance program (7356.843). 3. For reporting positron emission tomography (PET) postapproval inspections, use the PAC 56843 under this compliance program (7356.843). 4. When postapproval inspection coverage is concurrent with or expanded to provide inspection coverage under other compliance programs, follow the appropriate compliance program for inspection and report the coverage under separate captions in the establishment inspection report (EIR) in accordance with directions provided in the applicable compliance program. 		

FIELD REPORTING REQUIREMENTS:

1. Instructions for Firm Responses

The investigator instructs the firm’s management to submit Form FDA 483 responses to the designated Office of Pharmaceutical Quality Operations (OPQO) division in the Office of Regulatory Affairs’ (ORA’s) Office of Medical Products and Tobacco Operations (OMPTO), with a copy to the lead investigator. The investigator reviews the postapproval inspection portion of Form FDA 483 responses and, if inadequate, provides comments to ORA and to the Office of Pharmaceutical Manufacturing Assessment (OPMA) in the Center for Drug Evaluation and Research’s (CDER’s) Office of Pharmaceutical Quality (OPQ).

¹ In this compliance program, the terms *facility*, *firm*, *site*, and *establishment* are used synonymously.

2. Communication of Inspectional Results

The investigator completes the EIR—which includes the cover sheet, attachments, and exhibits—in eNSpect within established ORA time frames.² ORA notifies OPMA via the OPMA Postapproval Program mailbox (CDERPostApprovalProgram@fda.hhs.gov) when the EIR is available in an FDA electronic repository system.

3. Facility Alerts

- Enter a potential Official Action Indicated (pOAI) alert in Panorama no later than 2 business days after the inspection end date if significant current good manufacturing practice (CGMP) deficiencies were identified per Part V of compliance program 7356.002—*Drug Manufacturing Inspections* and the deficiencies could potentially impact marketed drug products.³

4. Inspection Classification

- Enter a No Action Indicated (NAI) classification in eNSpect if no deficiencies are noted.
- Enter a Voluntary Action Indicated (VAI) classification in eNSpect if deficiencies cited do not rise to the level of significance noted in Part V of this compliance program.
- Enter an Official Action Indicated (OAI) classification in eNSpect for:
 - PAC 56843 when significant deficiencies were identified for the subject drug per Part V of this compliance program.⁴
 - PAC 56002 when significant CGMP deficiencies were identified per Part V of compliance program 7356.002 and the deficiencies could potentially impact marketed drug products.

5. Firm Profile Class Code Update

Do not update the profile class unless at least one of the following applies:

- The drug product or active pharmaceutical ingredient (API) under inspection is the only drug product or API manufactured under that profile.

² See the ConOps agreement *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*, section 3.3, Communicating the Findings of the Inspection.

³ In rare cases, if significant CGMP deficiencies observed for the subject drug under Part V of this compliance program (7356.843) could potentially impact other marketed drugs but inspectional coverage was not expanded to compliance program 7356.002, a pOAI alert in Panorama should be entered no later than 2 business days after the inspection end date, as appropriate, in consultation with the ORA preapproval program manager. For conditions that recommend addition of coverage under compliance program 7356.002, see also Part II.3.E—Expanding Inspection Coverage to Compliance Program 7356.002.

⁴ Significant deficiencies can include CGMP deficiencies and application-related issues, which are further described in Part V of this compliance program.

- Surveillance coverage (compliance program 7356.002) is added to the postapproval inspection.

For inspections that are deemed acceptable following ORA's review (i.e., NAI or VAI for PAC 56843), ORA updates and finalizes PAC statuses and profiles, as appropriate, in eNSpect.

For inspections that are found initially unacceptable following ORA's review (i.e., initially OAI for PAC 56843), ORA enters the initial PAC status and profiles, as appropriate, in eNSpect and forwards to the lead CDER office, as described in Part V, for final review, classification, issuance of an FMD-145 letter, and modification in eNSpect.

6. Sample-Related Reporting Requirements

The designated analytical servicing laboratory in ORA's Office of Regulatory Science (ORS) uploads completed analytical worksheets to Compliance Management Services (CMS) and submits the original worksheet package to the ORA home district office of the manufacturing facility.

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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.⁵ In certain circumstances, FDA may approve applications without performing an inspection of the facility manufacturing the application product (e.g., the facility has a good CGMP compliance history, the application product is not a new profile class for the facility, the facility has a successful history with the manufacturing method being employed).

In 2002, FDA announced a significant initiative called Pharmaceutical CGMPs for the 21st Century to enhance and modernize the regulation of pharmaceutical manufacturing and product quality.⁶ This initiative 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 postapproval compliance program includes science- and risk-based approaches to the inspection of the firm's manufacturing process, product understanding, and quality controls; assurance of quality over the product lifecycle; evaluation of the firm's manufacturing capability; and verification of authenticity of the application data and conformance to approved application commitments.

In 2017, CDER and ORA entered the ConOps agreement *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations*, which outlines the roles and responsibilities of CDER and ORA for facility evaluation and preapproval, postapproval, surveillance, and for-cause inspections for human drugs. FDA components involved in this compliance program—CDER's OPQ and Office of Compliance (OC), ORA, and FDA laboratories—are committed to coordinating efforts and communications to resolve outstanding quality issues. This postapproval inspection compliance program aligns with this agreement.

To facilitate the management of postapproval chemistry, manufacturing, and controls (CMC) changes in a more predictable and efficient manner, FDA published the International Council for Harmonisation (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 2021.⁷ When used jointly with increased product and process knowledge—and in the context of the risk management principles in ICH guidance for industry *Q9(R1) Quality Risk Management* and an effective pharmaceutical quality system (PQS) as described in ICH guidance for industry *Q10 Pharmaceutical Quality System*—these guidance documents should enhance industry's ability to manage CMC changes effectively with less need for extensive regulatory oversight before implementation.

⁵ 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)).

⁶ See *Pharmaceutical Quality for the 21st Century—A Risk-Based Approach: Progress Report*.

⁷ When final, the ICH Q12 implementation guidance will represent FDA's current thinking on this topic. 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>.

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).⁸ 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 recommendations for how to report a broad set of postapproval changes.⁹ 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 postapproval inspection, 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 postapproval change management protocol (PACMP) and the product lifecycle management (PLCM) document, if submitted in the application. Under ICH Q12, PACMPs are regulatory tools that (1) describe CMC changes the applicant intends to implement during the commercial phase of a product's lifecycle; (2) propose the requirements and studies needed to implement product changes; (3) identify specific conditions and acceptance criteria to be met; (4) explain how changes would be prepared and verified, including assessment of the impact of the proposed change; and (5) suggest reporting categories to notify FDA. FDA refers to *PACMPs* as *comparability protocols*, which can be submitted independent of any prior identification of ECs in the original application or supplement.¹⁰ In all cases, changes are to be appropriately identified and implemented in accordance with CGMP requirements.

⁸ PAS=prior approval supplement; CBE=changes being effected.

⁹ 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*, *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports*, and *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA*.

¹⁰ *Comparability protocols* are synonymous with *protocols* as defined in 21 CFR 314.70(e) and 601.12(e). See guidance for industry *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA*.

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;¹¹ and (2) conducting remote regulatory assessments (RRAs),¹² 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.

¹¹ 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>.

¹² 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.

PART II—IMPLEMENTATION

1. Scope

ORA and CDER work together under this compliance program to evaluate marketed drug products manufactured under approved NDAs or ANDAs or their associated APIs (hereinafter *subject drugs*).¹³ Postapproval inspections are similar to preapproval inspections (PAIs) in that they are product-specific, but unlike PAIs, they are conducted after applications have been approved. Postapproval inspections for subject drugs are led by ORA with optional CDER participation.

A postapproval inspection focuses on process validation lifecycle, change management, changes submitted to the application, and execution of supporting activities per application commitments and CGMP requirements.¹⁴

This compliance program provides risk-based strategies for the scope of inspectional coverage and clarifies roles to establish efficient communication.

CDER uses information from postapproval inspections to update the lifecycle risk profile for a subject drug or to determine regulatory action.

2. Strategy

A. Risk-Based Determination for Postapproval Inspections

The IQA team¹⁵ uses a risk-based approach to product quality assessments, which includes facility evaluations and, if deemed necessary, inspections of manufacturing facilities listed in the application. During the review and approval of a marketing application, the IQA team assesses the potential risks concerning product, process, and facility and determines whether a postapproval inspection is needed. Such determinations are based on the totality of information that would indicate potential facility-relevant risks. In these cases, the ORA preapproval program manager (PAM) would consult with OPMA via the OPMA Postapproval Program mailbox (CDERPostApprovalProgram@fda.hhs.gov) to coordinate with the IQA team and confirm that a postapproval inspection is needed. In the absence of any potential concern for product quality from the IQA team or the ORA PAM based on their risk assessment of the application product, the

¹³ In this compliance program, the terms *API* and *drug substance* are synonymous.

¹⁴ For (a) PET drug products, refer to 21 CFR part 212 and compliance program 7356.002P—*Positron Emission Tomography (PET) CGMP Drug Process and Pre-approval Inspections/Investigations*; (b) drug products, refer to 21 CFR parts 210 and 211; (c) biological products, refer to 21 CFR parts 210, 211, 600, and 610; (d) APIs in general, refer to the recommendations in the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*; and (e) APIs labeled as sterile per compliance program 7356.002A—*Sterile Drug Process Inspections*, refer to 21 CFR parts 210 and 211.

¹⁵ For the purpose of this compliance program, the IQA team refers to a designated team of subject matter experts (e.g., drug substance assessor, drug product assessor, biopharmaceutics assessor, manufacturing assessor, ORA preapproval program manager or designee as needed) who are assigned to assess quality aspects of application submissions (i.e., original applications or postapproval submissions thereof). It may also include other roles, as needed. See the ConOps agreement.

manufacturing process, and the facility named in the application, a product-specific postapproval inspection of a facility may not be needed.

As appropriate, OPMA will identify additional assignments to those recommended by the IQA team based on the combined risk of the product, drug class, and dosage form and based on process and facility considerations. The overall purpose of this effort is to confirm that the risk to the patient from product quality issues is minimized.

The need for a postapproval inspection can be determined before, as well as after, application approval. For example:

- Before application approval, the IQA team may anticipate an increased risk of variability in product quality during scale up and sustained commercial production and decide that a postapproval inspection may be needed, instead of or in addition to a PAI. In these cases, either the IQA manufacturing assessment document or the final OPMA recommendation in Panorama Inspection View should indicate that a postapproval inspection should be performed.
- In some cases, concerns may arise during a PAI that will need to be addressed by a future postapproval inspection.
- After application approval, OPMA evaluates information from multiple sources in developing a list of postapproval inspection candidates. Sources can include completed IQA manufacturing assessments, assessments from OPQ's Office of Quality Surveillance (OQS) about the state of pharmaceutical quality at sites (e.g., site dossier), and any changes described in postmarket submissions.

B. Inspection by Objective

There are four primary product-specific objectives for postapproval inspections, each of which requires strategies that consider potential risks and identified concerns:

1. Objective 1: Process Validation Lifecycle and State of Control

Verify that there is a high degree of assurance that the commercial manufacturing process is in a state of control and consistently produces a subject drug that meets the applicable requirements for identity, strength, quality, and purity.¹⁶ Ensure that the firm's manufacturing process, control strategy, test methods, and process performance and product quality monitoring system for the subject drug are well-designed, implemented, validated as applicable, and verified throughout the product lifecycle as necessary.

2. Objective 2: Investigations and Corrective Action and Preventive Action (CAPA) Program

Determine whether investigations and CAPAs associated with the subject drug and associated processes and equipment were thoroughly evaluated and effectively implemented using quality risk management as an enabler in support of continual improvement.

¹⁶ See section 501(a)(2)(B) of the FD&C Act and 21 CFR 210.1(a) and 211.100(a).

3. Objective 3: Change Management, Change Effectiveness, and Conformance to the Application and Other Postmarketing Reports and Requirements

Determine whether implemented changes in the product, process, components, equipment, and/or facility associated with the subject drug were implemented effectively using quality risk management as an enabler in support of continual improvement. Verify that the subject drug is being manufactured in accordance with the approved application or active drug master file (DMF) referenced in the approved application, including filed postapproval changes. Confirm that the firm is fulfilling or is on track to fulfill commitments (e.g., providing additional stability data) made at the time of approval (of an original application or in subsequent submissions) and is meeting drug quality reporting requirements in a timely manner.

4. Objective 4: Integrity of Product Quality Data

Audit manufacturing controls, test results, and the related raw data for starting materials, in-process materials, and batches of the subject drug. Ensure that the test and production data are authentic, computed correctly, accurate, and documented per CGMP and that they support the associated decisions by the firm, application submissions, and lifecycle changes.

For details on inspectional and auditing techniques related to these objectives, refer to Part III—Inspectional.

3. Program Management Instructions

A. Facility Selection

OPMA selects a subject drug and associated manufacturing facilities as described in Part II.2.A—Risk-Based Determination for Postapproval Inspections. OPMA ensures that the manufacturing facility selected for postapproval inspection, including a facility named in a referenced DMF, is still named in an approved drug application. OPMA should, to the extent possible, confirm that the drug product is marketed using the Electronic Drug Registration and Listing System (eDRLS), Online Reporting Analysis Decision Support System (ORADSS), and the OQS site dossier, which may contain information useful for this determination.

B. Postapproval Inspection Assignment Requests

OPMA issues postapproval inspection assignment requests to the ORA Pharmaceutical Assignment mailbox (ORAPHARMAssignments@fda.hhs.gov) and the appropriate ORA division manager or ORA PAM. OPMA summarizes product and process knowledge from the application and identifies and advises on onsite coverage of potential risks to and concerns for product and process, which the investigator can use to develop an inspection plan.

These assignment requests could involve multiple applications for one facility, with different degrees of coverage of the four objectives. Reasons for the assignment could include the level of manufacturing experience, risk factors that apply to two or more subject drugs, and an efficient use of resources by covering multiple applications at one inspection, among others.

Postapproval inspection assignments should include the selection rationale, a product risk assessment based on the original application and postapproval submissions thereto, and the criteria for choosing applications, as necessary.

OPMA expects postapproval inspection assignments to be covered by ORA field personnel as part of ORA's work plan for the fiscal year. Resources allocated under PAC 56843 are intended for this compliance program. ORA notifies OPMA via the OPMA Postapproval Program mailbox (CDERPostApprovalProgram@fda.hhs.gov) if ORA will be unable to complete an assignment because of competing priorities.

ORA may find that the selected application product has not been marketed and may find a more suitable application product for postapproval inspection coverage. In these situations, ORA can exercise discretion and select a different application for postapproval inspection coverage than that assigned. However, ORA should coordinate with OPMA before making any such changes in assignment. A postapproval inspection may be combined with other programs or for-cause inspections as necessary for efficient inspection coverage. A systems-based CGMP surveillance inspection per compliance program 7356.002 may be added as per program management instructions. ORA should send concerns, problems, or objections regarding the assignment request to the OPMA Postapproval Program mailbox (CDERPostApprovalProgram@fda.hhs.gov).

C. Inspection Scheduling and Preparation

During logistics planning (e.g., determining the inspection start date), and before initiating the postapproval inspection, ORA may decide to confirm with the firm that the drug is manufactured at the inspection site.

In addition to following the steps in section 5.5.1.1—Preparation and References—of the *Investigations Operations Manual* (IOM), investigators should prepare for a postapproval inspection by conducting the following activities:

- Review the completed DMF/drug process/micro IQA reviews and the CMC section of the application (including the original development report), related supplements and postapproval changes, annual reports, application postapproval commitments, and related DMFs associated with the inspection assignment.

Note: This information can be accessed electronically via Panorama or DARRTS/Lorenz docuBridge. 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. ORA divisions are expected to establish a controlled access filing system to prevent the unauthorized use or release of application information.

- Based on the assignment request, contact the drug process, microbiology, and facility assessors assigned to the application, as applicable, to discuss special areas for coverage and questions regarding the submitted information (e.g., test methods, data tables, raw material attributes, justifications for finished product specifications).
- Access the application's most current PLCM document or comparability protocols via an OPMA request or docuBridge to ensure inspection coverage is relevant.

- After reviewing the assignment request and the related PAI's EIR (if performed), contact OPMA with questions about the application and contact the ORA PAM or designee with questions about the performed PAI, EIR, and firm history.
- In consultation with other inspection team members, develop an inspection plan that is specific to the establishment and its compliance history and to the subject drug being inspected and is consistent with this compliance program's objectives and inspectional and auditing techniques.

D. Inspection Team

ORA leads postapproval inspections and CDER participates with CDER and ORA management concurrence. ORA investigators and CDER application assessors or CDER subject matter experts are encouraged to jointly participate in postapproval inspections, particularly for those subject drugs that are a new molecular entity, incorporate a new molecular entity, are a novel formulation or dosage type, are produced using a novel unit operation or processing method, or use a novel analytical test method or technique. While the ORA investigator is responsible for reporting inspection findings in the EIR, all participants on an inspection team are responsible for submitting their portion of the EIR and supporting exhibits to the lead investigator in a timely manner, as directed by the lead investigator.

E. Expanding Inspection Coverage to Compliance Program 7356.002

The inspection team should add surveillance coverage with PAC 56002 under compliance program 7356.002¹⁷ if it finds objectionable conditions for the assigned subject drug during the postapproval inspection and if one of the following conditions exist:

- The subject drug is the only product manufactured at the establishment; or
- The objectionable conditions identified for the subject drug as per part V of this compliance program could potentially impact other marketed drug products manufactured at the establishment.

F. CDER Consultation During Inspection

When product-specific issues arise that cannot be immediately resolved by the investigator on-site and may need the subject matter expertise of product assessors from CDER (OPQ), ORA can reach out to the appropriate OPMA/review division representative for clarification.

¹⁷ Unless there is an assignment from the current Site Surveillance Inspection List or there is justification based on objectionable observations that could impact marketed drug products, surveillance coverage (56002(X)) would not typically be added to postapproval inspection assignments.

G. Refusals

Under section 501(j) of the FD&C Act, a drug is adulterated that “has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection.”¹⁸

Investigators should fully document the circumstances of the denial, delay, limitation, or refusal as outlined in the IOM. The ORA program division should attempt to resolve the issue, but if initial attempts are unsuccessful, the ORA program division should notify its Office of Chief Counsel senior enforcement advisor, if needed, and OC for awareness and assistance. In the event a denial, delay, limitation, or refusal occurs during an inspection where the circumstances indicate a significant threat to humans or animals, the investigator should attempt to collect an inventory of all drugs (components and finished products) at the establishment.

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 postapproval inspection 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 where 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.

¹⁸ See also guidance for industry *Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* for additional information.

PART III—INSPECTIONAL

1. Inspection/Audit Strategy

There are four primary product-specific objectives to be covered under this compliance program:

1. Objective 1: Process Validation Lifecycle and State of Control.
2. Objective 2: Investigations and CAPA Program.
3. Objective 3: Change Management, Change Effectiveness, and Conformance to the Application and Other Postmarketing Reports and Requirements.
4. Objective 4: Integrity of Product Quality Data.

The inspection team should provide the coverage described in the assignment memo as well as provide additional, in-depth coverage of potential issues identified during the inspection.

2. Inspection/Audit Coverage, Objectives, and Techniques

Subsequent to an application approval, the firm should have generated and collected substantially more manufacturing and laboratory data than what is typically provided at filing and made available during the application review. Product and process knowledge gained by analysis of such data should help firms demonstrate their ability to consistently maintain process controls, meet quality specifications, reliably produce subject drugs of intended quality, and adequately respond to unexpected or aberrant results in a timely manner to prevent poor quality drug products from reaching consumers.

Postapproval inspection focuses largely on the product lifecycle, including the process validation lifecycle and manufacturing changes that may have occurred after approval. During a postapproval inspection, the inspection team reviews records and processes for changes related to the subject drug that have occurred from the time the application was approved up to the time of the inspection. The inspection team should also confirm that manufacturing-related commitments made by applicants during the application or supplement approval stage have been completed or are underway. It is not uncommon for manufacturers to change production equipment, manufacturing procedures, and associated control strategies based on scale-up, process qualification, process verification, and capacity needs. Such modifications, which generally need to be submitted for FDA review (see 21 CFR 314.70) unless otherwise provided for as approved ECs, reflect changes to the approved application and must conform to CGMP regulations (see 21 CFR 211.22 and 211.100).

This section further explains each postapproval inspectional objective and provides examples of documents and processes to review, guiding points for inspectional focus areas and coverage, a framework for assessing the firm's performance, and references to applicable regulations and guidance documents.

A. Objective 1: Process Validation Lifecycle and State of Control

Summary: Verify that there is a high degree of assurance that the commercial manufacturing process is in a state of control and consistently produces a subject drug that meets the applicable requirements for identity, strength, quality, and purity.¹⁹ Ensure that the firm's manufacturing process, control strategy, test methods, and process performance and product quality monitoring system for the subject drug are well-designed, implemented, validated as applicable, and verified throughout the product lifecycle as necessary.

Process validation is defined as the collection and evaluation of data from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation is grouped into three stages: (1) process design, (2) process qualification, and (3) continued process verification.²⁰ Process validation coverage during postapproval inspection primarily focuses on stages 2 and 3—process qualification and continued process verification—for the commercial manufacture of the subject drug. Stage 1—process design—is expected to require less coverage, particularly for subject drugs for which PAIs were conducted. During a postapproval inspection, the investigator may need to evaluate certain aspects of process design if they observe variability in commercial manufacturing data (stage 3 data, e.g., trends, deviations, failures) or process qualification studies and data (stage 2 data).

Suggested focus areas within the three process validation stages are described below.

(1) Objective 1A: Review of Process Design (Process Validation—Stage 1)

Sufficient documentation of process design activities is necessary to ensure that process knowledge is appropriately captured, evaluated, and leveraged for use in subsequent stages of process validation. Product development activities, including design of experiment (DoE) studies and appropriate application of risk analysis tools in particular, are perhaps among the best industry practices that manufacturers can use to develop process knowledge.

Process design and development studies, in particular DoE studies, typically help reveal relationships between variable inputs (e.g., component characteristics, process parameters) and resulting outputs (e.g., in-process material, intermediates, subject drug). Additionally, process design studies (e.g., laboratory or pilot-scale models, computer-based or virtual simulations of certain unit operations or process dynamics), and in particular the scale-up studies to commercial production, address the functionality and operational limitations of commercial equipment and the anticipated contributions to variability posed by different component lots (e.g., impact of component particle size on unit operations such as mixing/blending, filling, or compression), production operators, environmental conditions, and measurement systems in the production setting. The scientific data resulting from process design, including DoE studies, can contribute to process understanding and

¹⁹ See footnote 16.

²⁰ See guidance for industry *Process Validation: General Principles and Practices* for expectations about the scope and purpose of these three stages.

thereby help manufacturers justify ranges for incoming component quality, equipment parameters, in-process material quality attributes, and the design of manufacturing process and controls.

Inspection Coverage²¹

- If objective 1A was not previously evaluated (e.g., during a PAI or during an RIE²² or an assessment conducted under section 704(a)(4) of the FD&C Act), or there was a quality concern identified from the previous evaluation, review the product development activities, experimental reports, and other supportive data and reports available—whether they were included in the original application or they were performed as part of a research or trial batch on a different manufacturing scale—to determine if the process was designed to produce the subject drug meeting the established critical quality attributes before the firm initiated stage 2 process validation activities.
- Determine if the firm appropriately executed relevant process design activities in response to deviations observed in stage 2 or 3.

(2) Objective 1B: Review of Process Performance Qualification (Process Validation—Stage 2)

The focus of postapproval inspections during the process qualification stage is on process performance qualification (PPQ), which is primarily concerned with achieving a level of confidence that the commercial process and controls consistently result in high-quality product and that commercial distribution is justified.

Firms can achieve this by (1) designing and executing a written protocol (hereinafter *PPQ protocol*) that specifies manufacturing conditions, controls, testing, and expected outcomes, and (2) generating a report (hereinafter *PPQ report*) that documents adherence to the PPQ protocol and draws conclusions as to whether the process (a) meets the conditions established in the PPQ protocol and (b) is in a state of control.²³

Inspection Coverage

- Verify that the PPQ protocol for the subject drug has been reviewed and approved by appropriate departments, including the quality unit, before its execution as per the established procedure.
- Evaluate the adequacy of the PPQ protocol in terms of the essential elements it describes, which may include but are not limited to the following:

²¹ Refer to the original application and IQA for information regarding manufacturing of the drug substance or drug product, batch formula and components, unit operations, process development activities, in-process controls and specifications, and identified lifecycle considerations.

²² For more information on this topic, see guidances for industry *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency* and *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency: Questions and Answers*.

²³ For further details, see guidance for industry *Process Validation: General Principles and Practices*.

- A reflection of the approved application.
- Primary features and layout of the commercial production facilities.
- Qualifications of utilities, equipment, raw material (including starting materials), components, and personnel.
- Description of manufacturing conditions, identification of relevant quality attributes, including critical quality attributes, along with description of their controls.
 - Acceptance criteria for each significant processing step and for the cumulative process.
 - Identification of the data to be collected and a description of when and how it will be evaluated.
- Limitations for proposed commercial manufacturing conditions, including equipment operating parameters and processing limits.
- Identification and validation status of test methods used for process measurements (e.g., in-process, release testing).
- A representative sampling plan including sampling points, sampling strategy (frequency and number), and acceptance criteria with an objective to provide sufficient statistical confidence of quality both within a batch and across batches.²⁴
- Provision for addressing deviations from expected conditions and handling of nonconforming data.
- Documentation of science-based justification if excluding PPQ data from further consideration.
- Evaluate the adequacy of the information summarized in the PPQ report, which may include but is not limited to the following:
 - Summary and analysis of data collected, as specified by the PPQ protocol.
 - Evaluation of unexpected observations and additional data not specified in the PPQ protocol.
 - Summary and discussion of manufacturing nonconformances such as deviations, aberrant test results, and other information that may have a bearing on the validity of the process.
 - Description in sufficient detail of corrective actions or changes that need to be made to existing procedures and controls.
 - A conclusion that is based on a compilation of process knowledge and information from the design stage through the process qualification stage and includes the following:

²⁴ For FDA's current thinking regarding sampling for blend uniformity/content uniformity, see <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#16> rather than relying solely on the requirements of USP General Chapter <905> *Uniformity of Dosage Units* or EP 2.9.6 *Uniformity of Content of Single-Dose Preparations* without performing additional developmental activities. USP= United States Pharmacopeia; EP= European Pharmacopeia.

- Clear establishment of the degree to which PPQ protocol study conditions, acceptance criteria, and process performance indicators for product quality and process consistency have been met, including a description of the control of and justification for changes made to PPQ criteria during the study.
- Sufficient description of manufacturing conditions or quality attributes identified during the PPQ study that, per a risk analysis, will require either correction or changes to existing procedures and controls.
- Conclusion as to whether the process is in a state of control. If not, the report should describe the conditions to be met before such a conclusion can be reached.
- Approval of the PPQ report by appropriate department and quality unit personnel.
- Determine whether the conclusions on the manufacturing process' state of control and commercial distribution are justified and supported by the information in the PPQ report.
- Determine the accuracy and authenticity of the data and calculations generated during execution of the PPQ protocol (e.g., raw data including laboratory notebooks, executed batch records, internal quality decisions). Evaluate and determine the adequacy of the executed PPQ protocol and the final written report, including deviations, results, outcomes, and conclusions drawn.
- Evaluate the investigation reports for the firm's resolution of product quality/process control issues that arose during the PPQ study (e.g., specifications not met, process controls not adequate, variability exceeding acceptance criteria, lots rejected).²⁵
- Evaluate the impact of recent changes to commercial manufacturing facilities, processing conditions, or critical quality attributes in the approved application on the validity of the PPQ study.
- Evaluate whether the equipment and utilities remain suitable for their intended use and whether the preventive maintenance program remains appropriate based on information collected since PPQ completion.

(3) Objective 1C: Review of Continued Process Verification (Process Validation—Stage 3)

Continued process verification provides assurance throughout the lifecycle that the commercial scale process remains in a state of control (i.e., the validated state). During continued process verification, manufacturers enhance, as necessary, mechanisms for detecting and monitoring signals of process drift, shift, or loss of control to identify the source and scope of newly identified variations. Manufacturers evaluate the commercial process and product data to identify and prevent unacceptable variability. As manufacturers accumulate information during commercial production,

²⁵ An unresolved PPQ processing issue may allow for variation in process parameters or in commercial product quality that unexpectedly becomes unacceptable. The source of an unresolved PPQ processing issue may be a hitherto unidentified process design (stage 1) defect. An unresolved PPQ processing issue may allow for episodic or persistent process variation in process parameters or in product quality that is revealed by a careful inspection of commercial product data and information (stage 3).

component variability that was not observed during process design and development (stage 1) or PPQ (stage 2) can manifest in the in-process materials and thereby contribute to variability in product quality. When variability is detected, manufacturers should investigate and determine if process parameter ranges need to be adjusted, process changes are needed to manage the variability, or increased sampling is needed to better monitor and understand in-process material attribute variability. Changes in operating conditions (e.g., ranges/set-points), process controls, components or in-process material attributes/characteristics, and specifications may require additional process design or PPQ studies to maintain compliance with 21 CFR 211.180(e) and sections 506A(a)(1) and (b) of the FD&C Act.

Inspection Coverage

- Review and evaluate the firm's quality management oversight and the methods used to assess the commercial product data; determine if the firm adequately detects emerging trends related to product quality from the information found in product data analysis reports; and determine if the firm adequately incorporates risk analysis into decisions regarding continued process verification data. This information may be found in:
 - Analysis of nonconforming product data from complaints, product rejections, recalls, NDA/ANDA field alert reports (FARs), adverse event reports, audits, regulatory inspections, and similar sources.
 - Investigations into unexpected trends recognized from the analysis of process, material, or product variability.
 - Process performance and product quality monitoring data, including control charts, process deviations, in-process batch release testing results, process yield variations, nonconformances, and batch records.
 - Documentation of the appropriate statistical process control techniques applied as part of the product and quality improvement program.
 - Laboratory records, including stability data trend analysis and reports, testing deviations, nonconformances, investigations, and CAPA reports²⁶ with discussions of root cause factors for out-of-trend (OOT) and out-of-specification (OOS) test results for raw materials, in-process materials, and the subject drug.
- Determine if the firm adequately considered the need for additional process design or process qualification studies when changes are made to the process after the initial PPQ, including necessary adjustment of the sampling plan (e.g., frequency, sample size, location) to better monitor and understand process variability.
- Determine if the firm evaluates production data and leverages such data to identify changes needed in the manufacturing process, control procedures, or specifications, thereby promoting continual improvement throughout the product lifecycle.

²⁶ Refer to objective 2 regarding important elements to be considered for investigations and CAPAs.

(4) Related Resources

Regulations

- 21 CFR 211.22, 211.63, 211.84, 211.100, 211.110, 211.180

Guidance for Industry

- *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015)
- *Control of Nitrosamine Impurities in Human Drugs*, Rev. 1 (February 2021)
- *Data Integrity and Compliance With Drug CGMP Questions and Answers* (December 2018)
- *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency: Questions and Answers* (May 2021)
- *Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs* (April 2012)
- *PET Drugs—Current Good Manufacturing Practice (CGMP)* (December 2009)
- *PET Drugs—Current Good Manufacturing Practice (CGMP), Small Entity Compliance Guide* (August 2011)
- *Process Validation: General Principles and Practices* (January 2011)
- *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006)
- *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency* (April 2021)
- *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (October 2004)

Draft Guidance for Industry²⁷

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

ICH Guidance for Industry

- *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016)
- *Q8(R2) Pharmaceutical Development* (November 2009)
- *Q9(R1) Quality Risk Management*, Draft (June 2022)
- *Q10 Pharmaceutical Quality System* (April 2009)
- *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021)

²⁷ When final, this guidance will represent the FDA's current thinking on this topic.

B. Objective 2: Investigations and CAPA Program

Summary: Determine whether investigations and CAPAs associated with the subject drug and associated processes and equipment were thoroughly evaluated and effectively implemented using quality risk management as an enabler in support of continual improvement.

(1) Objective 2A: Investigations

In general, the depth and breadth of investigations of any product- or process-related deviation should be governed by a documented risk assessment and should take a structured approach to determining the root cause of the deviation.

The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk. The firm should support its conclusions with scientific rationale and data generated through investigations. Where applicable, the firm should use retain samples or confirmatory testing to aid in its investigations. Laboratory error should be rare and is not sufficient to justify invalidating data, unless there is clear evidence that it was the root cause of a failing result.

The analysis of product risk should be commensurate with the significance and risk of the nonconformity and its perceived impact on the quality, safety, or effectiveness of the drug product. The firm should conduct the risk assessment in a timely manner, using sound scientific and quality risk management principles. This includes consulting subject matter experts from departments within the organization with the expertise needed to ensure a full understanding of the scope of the problem and its implications for product quality and risk to public health.²⁸

Inspection Coverage²⁹

- Review the firm's response to both internal (e.g., deviation, OOT, OOS, errors) and external (e.g., drug quality reports, recalls, complaints) signals for the subject drug. Investigations involving released drug product should be given priority.
- Ascertain if the firm conducts or has conducted a thorough root cause investigation to identify product quality issues for the subject drug.
- Determine if the firm's investigations included an analysis of product risk and an evaluation of risk to public health.
- Confirm that the firm expanded the scope of the investigation to include any and all lots of the subject drug and any other drug products that may have been affected.

²⁸ Departments include those involved in pharmaceutical development, manufacturing, quality, technical services, laboratory work, materials management, regulatory affairs, and medical services.

²⁹ During a postapproval inspection, coverage should focus on the investigations and CAPAs pertaining to the subject drug rather than on the overall effectiveness or validity of the investigation system itself, which is the typical focus of a surveillance-based inspection.

(2) Objective 2B: CAPA Program

The CAPA program considers the risk that the problem poses to product quality. The level of effort, formality, and documentation of CAPAs should be commensurate with the level of risk. The CAPA program should also address identified problems, prevent their recurrence, and trigger improvements through change management as necessary.

Inspection Coverage

- Based on the firm's response to internal and external signals for the subject drug, check whether the firm has a procedure to prioritize CAPAs based on risk and manage CAPAs for the released subject drug in a timely manner. Through this coverage, assess the adequacy of the firm's approach, actions, and responses regarding the following:
 - Routine, proactive identification and analysis of quality data regarding product and quality problems.
 - Evaluation of deviations, nonconformances, investigations, complaints, Process Performance and Product Quality Monitoring System data/trends, and other external reports to determine an appropriate CAPA.
 - Documentation of the full extent of a problem before conducting risk analysis or determining the proper course of a CAPA.
 - Application of quality risk management concepts in the CAPA approach.
 - Review of proposed CAPAs by a cross-functional team with the necessary training and experience before management approval.
- Evaluate the firm's CAPAs to ensure they were implemented in a timely manner and that they are effective and prevent recurrence. Through this coverage, assess the adequacy of the firm's CAPA approach, actions, and responses regarding the following:
 - Documentation of effectiveness check criteria (e.g., implementation timeline and milestones, collection of feedback, validations, other evidence of the success of the corrections made).
 - Monitoring for recurring deviations.
 - Evaluation and mitigation of new or recurring risks derived from the CAPA effectiveness check, with management review and approval.
 - Management assurance that responsible parties will follow through on CAPA commitments, including reporting as postapproval changes, as applicable.
 - Timely filings of regulatory submissions and postmarketing reports.

(3) Related Resources

Regulations

- 21 CFR 211.22(c), 211.84, 211.100, 211.110(a)

Guidance for Industry

- *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017)
- *Investigating Out-of-Specification Test Results for Pharmaceutical Production* (October 2006)
- *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006)

ICH Guidance for Industry

- *Q9(R1) Quality Risk Management*, Draft (June 2022)
- *Q10 Pharmaceutical Quality System* (April 2009)

C. Objective 3: Change Management, Change Effectiveness, and Conformance to the Application and Other Postmarketing Reports and Requirements

Summary: Determine whether implemented changes in the product, process, components, equipment, and/or facility associated with the subject drug were implemented effectively using quality risk management as an enabler in support of continual improvement. Verify that the subject drug is being manufactured in accordance with the approved application or active DMF referenced in the approved application, including filed postapproval changes. Confirm that the firm is fulfilling or is on track to fulfill commitments (e.g., providing additional stability data) made at the time of approval (original application or subsequent submissions) and is meeting drug quality reporting requirements in a timely manner.

It is not uncommon for manufacturers to change facilities (e.g., add a new facility or replace an existing facility), introduce changes within a facility, or change production equipment or manufacturing and control procedures because of scale-up, process qualification, process verification, capacity needs, or improvement plans. The impetus for change may originate from internal sources (e.g., the outputs of process performance and product quality monitoring, CAPAs, product reviews, audits, adverse trends, OOS results, adoption of advanced manufacturing) or external sources (e.g., adverse event reports, FDA inspections, compendia modifications). Change management ensures the appropriate execution of changes so that information relevant to the subject drug is fed back into the process and control strategy to effect continual improvement and ensure the maintenance of a state of control.

A change management system:

- Controls and implements proposed changes that are expected to improve product quality, process performance, and robustness.
- Ensures that proposed changes that might impact product quality (and thereby potentially product safety, effectiveness, or both) are evaluated commensurate with the level of risk to patients by using sound scientific and quality risk management principles.

- Documents how the assessed risk was categorized and how it will be managed, controlled, or mitigated in the event the proposed change is not implemented.
- Ensures that implementation takes place in a timely manner with the approval of the quality unit.
- Monitors the effects of changes to ensure that they have the intended effect and that there are no unintended consequences.

The change control process should involve input from departments with the expertise needed to assess the specific change and to ensure a full understanding of the scope of the change and its implications for the process and control strategy.

Subject matter experts from the relevant departments responsible for implementing a specific change determine the type and extent of data (existing or to be newly generated) needed to support the change, and develop study protocols describing the methods, prospective acceptance criteria, and additional post-implementation process performance or product quality monitoring as necessary.

As mentioned above, the change control process should also verify that changes have been effective in achieving the desired outcome with no unintended consequences. For example, a sufficient number of post-implementation commercial batches may be identified for review and evaluation. As another example, increasing data-gathering efforts (e.g., evaluating stability batches), as needed, confirms that the change objectives are achieved, that there is no deleterious impact on product quality, and that the knowledge gained is captured. The impact of each implemented change should be evaluated before the affected batches are released.

During a postapproval inspection, coverage should focus on changes pertaining to the subject drug under evaluation rather than on the overall effectiveness or validity of the change control or change management system, which is the typical focus of a surveillance-based inspection.

(1) Objective 3A: Change Management and Change Effectiveness

The change management system ensures that appropriate science- and knowledge-based risk assessments are performed and documented for changes, taking into account the points below:

- The level of rigor, effort (e.g., testing, validation, review), and documentation is commensurate with the level of risk associated with each change, and each change is appropriately categorized according to the associated level of risk as defined by the site.
- Risk assessment adequately evaluates the potential risks and benefits of changes to product quality, safety, and effectiveness.
- Changes and their risks are assessed using current product and process knowledge, including appropriate data (available or generated, if needed), to identify current and needed risk controls for each change.

The change management system also ensures that appropriate time and effort have been considered in change planning, prioritization, and implementation, taking into account the points below:

- The outcomes of risk assessments and the assigned risk levels drive change planning, prioritization, and implementation expectations.

- Data to support the change, as well as acceptance criteria and change effectiveness criteria, are predefined in change planning. These may include continued process verification and statistical assessments, including process capability and process performance indices—Cpk and Ppk—to aid with the quantitative assessment of risk control.
- Risks with the current state (until changes are implemented) and risks that might be temporarily introduced during the change process are adequately assessed.
- Interim controls (short-term measures) are identified and implemented in a timely manner to monitor and mitigate risks associated with the current state.
- Identified risk control measures are adequately implemented in a timely manner.
- Approval to proceed with change implementation or rejection of the change is documented with appropriate justification.
- Relevant risk assessments are reviewed and are updated after the implementation of changes.
- Relevant and timely updates are made to regulatory filings, when appropriate (e.g., annual reports must include all changes of relevance to filings; see 21 CFR 314.81 and 314.98).

In addition to general inspection coverage considerations regarding change management and effectiveness, this section includes considerations covering product quality review (PQR) through the PQS as an input to change management, ECs, comparability protocols, PLCM documents, and supply chain-related changes.³⁰ For example, changes in the supply chain for APIs, excipients, and primary packaging components that occur after approval should be thoroughly evaluated, approved, and documented to ensure that they are unlikely to pose an adverse risk to product quality and thereby to patients.

Inspection Coverage

- Evaluate changes to facility, product, process, and practices that have occurred since the application was approved, or since the last inspection providing coverage of changes for this product, that may have affected product quality. Evaluate the scientific justification for and implementation of the changes and compare them to the changes contained in postapproval submissions.
- Determine whether:
 - The factors or reasons triggering changes and the related evidence are clearly documented.³¹

³⁰ See ICH Q12. The PQR is also referred to as an *annual product review*, which is a regulatory requirement per 21 CFR 211.180(e).

³¹ Examples of common lifecycle factors that trigger change include but are not limited to the following: upgrades to equipment or facilities; changes in raw material quality or sourcing; improvements in manufacturing performance and consistency (to reduce variability, improve yield, etc.); enhancements in manufacturing capacity; corrections of quality issues; and addressing of signals from the PQS such as deviations, complaints/adverse events, CAPAs, product quality review, operational review metrics, management review, new regulations, compliance gaps, implementing innovation, and continual improvement initiatives.

- Proposed changes for the subject drug have been adequately evaluated using quality risk management principles³² and have been validated (if needed) and approved for implementation through a formal change control system.
- Proposed changes have been adequately justified with a scientific rationale and data. Confirm that the evaluation of each change has been completed before affected batches were released.³³
- Relevant experts and stakeholders (e.g., subject matter experts, specific departments) are involved in change proposal development and approval.³⁴
- The objectives, scope, expected outcomes, and anticipated benefits of proposed changes are documented.
- Changes are proposed and formally evaluated in a timely manner, and a decision to accept or reject the proposal is documented. For rejected change proposals, the rationale for rejection is adequately documented.
- Before change closure, the firm has ensured that:
 - Changes have met their intended objectives and predefined effectiveness criteria. Deviations from those criteria are adequately assessed, approved, and managed or justified. Whenever possible, quantitative data are leveraged to objectively determine change effectiveness (e.g., statistical confidence and coverage).
 - As part of the quality risk management activities, residual risks are assessed and managed to acceptable levels, and appropriate adaptations of procedures and controls are implemented.
 - Unintended consequences or risks introduced as a result of changes are evaluated, documented, approved, handled adequately, and are subject to a predefined monitoring time frame.
- Before or after change closure, the firm has ensured that:
 - Post-implementation actions (including those for deviations from predefined acceptance criteria or CAPAs) are identified and completed adequately.
 - Relevant risk assessments are updated after changes are implemented and their effectiveness is assessed. New product/process knowledge resulting from risk assessments are captured in the appropriate quality and operations documents (e.g., standard operating procedures, reports, product control strategy documents).

³² See ICH Q9(R1), and Annex II in particular. Bear in mind that an impact assessment, typically performed within the change control system, may not be as comprehensive as a risk assessment for proposed changes. Impact assessments often assign categorization and determine the change's regulatory filing but may not always fully address what might go wrong or would be improved in the context of current product and process knowledge, the control strategy, and the product lifecycle.

³³ See footnote 32 with regard to impact assessment.

³⁴ See footnote 28.

- The effects of implemented changes are actively monitored (e.g., use of additional samples for in-process or stability testing, review of data results after completion of a prespecified number of batches) to confirm that change objectives are achieved and that there is no deleterious impact on product quality.
- Changes are monitored via ongoing monitoring systems to ensure maintenance of a state of control,³⁵ and lessons learned are captured and communicated. When deviations associated with postapproval changes are detected:
 - Risk-mitigating steps are developed in the case of deviations from acceptance criteria or identification of unanticipated risks.
 - The issue is managed via the firm’s deviation management process and appropriate CAPAs are identified and undertaken via the firm’s CAPA program.
- Confirm that implemented changes, as appropriate, were captured and assessed as part of the PQR procedures, which are described in further detail under objective 3B in Part III.2.C(2) of this compliance program. (Also see “Inspection Coverage—Pharmaceutical Quality System Assessment” below.)

Inspection Coverage—Pharmaceutical Quality System Assessment

- Through the review of PQR procedures, confirm that senior management is responsible for PQS governance through periodic management review to ensure its continuing suitability and effectiveness.³⁶ When confirming that periodic management reviews are occurring:
 - Determine whether management reviews include:
 - Measurement of achievement of PQS objectives.
 - Assessment of performance indicators used to monitor the effectiveness of processes within the PQS (e.g., complaints, deviations, CAPAs, self-assessments, external assessments).
 - Determine whether outcomes of management review of the PQS and monitoring of internal and external factors include:
 - Improvements to the PQS and related processes.
 - Allocation or reallocation of resources and personnel training.
 - Revisions to quality policy and quality objectives, as appropriate.
 - Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management.

³⁵ The inspection coverage related to state of control under this objective may overlap with the inspection coverage recommended for stages 2 and 3 of process validation under objectives 1B and 1C, respectively.

³⁶ See ICH Q10.

Inspection Coverage—Comparability Protocols and Product Lifecycle Management

- Determine whether the applicant has an approved comparability protocol or specified and/or categorized postapproval changes in a PLCM document.
 - If there is an approved comparability protocol, verify the implementation status of any change.
 - Review that the change as implemented aligns with the comparability protocol.
 - Verify whether the data generated demonstrate that the change objective and acceptance criteria were met.
 - If there is an approved PLCM document:
 - Verify that changes to all ECs are handled per the approved PLCM and changes to parameters unrelated to ECs are managed appropriately under the firm’s PQS.
 - Verify the maintenance status of the document in terms of when and how the document is updated.
 - Review that the document was updated after the change was implemented to capture new product/process knowledge gained during implementation.
 - Verify whether subsequent regulatory filings for the subject drug have been included in the document.
- If the applicant/manufacturer is not using an approved PLCM document for the subject drug, assess and report whether the changes are being reported in a manner that is consistent with the appropriate regulations (see 21 CFR 314.70 and 314.97) and guidance documents³⁷ to provide continued assurance of quality for the subject drug over the product lifecycle.

Inspection Coverage—Supplier/Vendor Qualification and Agreements Assessment

- Assess the adequacy of the firm’s supplier qualification program by ensuring that the firm:
 - Evaluated supplier changes for the raw materials, intermediates, or components of the subject drug, as applicable, using the site change management system, evaluated the risk of the supplier change before implementation, and evaluated the quality of the drug and its individual characteristics (such as the impurity profile).
 - Evaluated changes to individual raw material and qualified component suppliers before authorizing the material from those suppliers for use, and reevaluates the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals.
 - Maintains defined sampling plans for components to obtain samples that are representative of the shipment and defined acceptance levels to detect unacceptable component variability.

³⁷ See footnote 9.

- Has appropriate controls in place to measure and control variability, such as by periodically challenging the accuracy of the certificate of analysis via performing independent confirmatory testing at a defined frequency.
- If the firm has a quality agreement in place with other facilities, including drug applicants, for either critical inputs (e.g., ingredients, raw materials) or outputs (e.g., bulk API for micronization, bulk in-process material or bulk finished product for further processing such as packaging), confirm that it defines communication roles and CGMP responsibilities of suppliers, contract manufacturers, and drug manufacturers regarding the notification and impact of changes in or deviations from processes or acceptance criteria for the inputs or outputs.

(2) Objective 3B: Conformance to the Application and Other Postmarketing Reports and Requirements

In accordance with statutory and regulatory requirements,³⁸ applicants must notify FDA of manufacturing changes to approved applications before distributing drug products made with such changes. Under 21 CFR 314.70 and 314.97, applicants must notify FDA about changes made to the conditions and the variations in the conditions that were established in approved applications. These regulations identify three broad reporting categories: *major changes*, which require submission of a prior approval supplement (PAS); *moderate changes*, which require submission of a changes being effected in 30 days (CBE-30) supplement or a CBE-0 supplement; and *minor changes*, which must be reported in an annual report. The reporting category for a change is based on the potential risk for the change to have an adverse effect on the identity, strength, quality, or purity of the drug product as these factors may relate to its safety or effectiveness. If an application includes approved ECs with specified reporting categories (see Part 1—Background), the reporting category reflected in the PLCM document is considered the appropriate submission type for a postapproval change to that EC.

Applicants of NDAs and ANDAs are required to file FARs for relevant quality issues concerning distributed product batches pursuant to 21 CFR 314.81. A failure to file a report is considered a significant violation and subject to a Form FDA 483 citation.³⁹

Firms conduct periodic PQRs—annually at a minimum or more frequently on a rolling basis—to verify reliability and performance of the existing process in delivering quality product, verify the appropriateness of current specifications for raw materials (including starting materials), components, and the subject drug, and identify trends in product quality and process performance that warrant change.⁴⁰

PQRs, taking into account previous reviews, include at least the following for the subject drug, as applicable:

³⁸ See section 506A of the FD&C Act (21 U.S.C. 356a).

³⁹ See compliance program 7356.021—*Drug Quality Reporting System (DQRS) (MedWatch Reports) NDA Field Alert Reporting (FARs)* and guidance for industry *Field Alert Report Submission: Questions and Answers*.

⁴⁰ See 21 CFR 211.180(e).

- Review of quality specifications for raw materials, intermediates, components, container closure systems, and packaging materials as pertain to the subject drug, especially those from new sources.
- Review of supplier qualification or requalification reports for supplied materials, components, or other outsourced contract manufacturing activities or services.
- Review of critical in-process controls, tests, in-process specifications, test results for in-process materials, and the final specifications and test results for the subject drug.
- Review of batches that failed to meet established specifications and their related investigations.
- Review of significant deviations or nonconformances, their related investigations, and the effectiveness of resultant CAPAs taken.
- Review of changes to processes or analytical methods.
- Review of supplements approved or issued a complete response action.
- Review of the results of the stability monitoring program and adverse trends.
- Review of quality-related returns, complaints, and recalls and the investigations performed at the time.
- Review of the adequacy of previous product process or equipment corrective actions.
- The qualification status of relevant equipment and utilities (e.g., HVAC, water, compressed gases).

Inspection Coverage⁴¹

- Review the timeliness of notification via FARs for issues that have the potential to impact product on the market.
- Evaluate the status of defined postmarketing commitments or postmarketing reporting requirements that the applicant had agreed to fulfill in a timely manner as part of the authorization for the initial approval of the NDA.⁴²
- Review changes that have been implemented since approval for the drug product and determine whether the changes were properly reported to FDA.
- Evaluate if the firm has underestimated changes in terms of their potential impact on product quality and type of change to the regulatory filing (e.g., as a minor change requiring an annual report submission instead of as a moderate change requiring a CBE-30 supplement).

⁴¹ See footnote 21.

⁴² *Postmarketing commitments* are otherwise known as *quality postmarketing agreements* (QPAs) as defined in the draft guidance for industry *Benefit-Risk Considerations for Product Quality Assessments. Postmarketing reporting requirements* refer to “Other postmarketing reports” as required under 21 CFR 314.81—in particular 314.81(b)(2)(iv), (vii), (viii), and (ix) for NDAs—and the same for ANDAs under 21 CFR 314.98—in particular 314.98(c).

- Evaluate if the firm manufactured and improperly distributed any batches with changes that required prior FDA approval.
- Determine whether manufacturing is consistent with what was included in the application (e.g., if manufacturing and analytical equipment, manufacturing process, process controls, in-process and release tests, specifications, and methods employed are the same as those documented in the application).
- Confirm and as necessary report back whether the commitments made by the applicant, at the time the application or application supplement was approved, have been completed or are underway.
- Verify that the firm:
 - Evaluates PQR results and assesses whether to undertake CAPAs, change proposals, or process revalidation for continual improvement.
 - Uses quality risk management to evaluate proposed CAPAs, changes, or process revalidation.
 - Completes actions that are undertaken as a result of a PQR in a timely and effective manner.
 - Has procedures for the ongoing management and review of actions undertaken as a result of PQRs and verifies the effectiveness of these procedures during self-inspection.
 - Reviews the effectiveness of actions undertaken as a result of a PQR at the next PQR.

(3) Related Resources

Regulations

- 21 CFR 211.198, 310.305, 314.70, 314.80, 314.81, 314.97, 314.98

Guidance 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)
- *Changes to an Approved NDA or ANDA: Questions and Answers* (January 2001)
- *CMC Postapproval Manufacturing Changes for Specified Biological Products to be Documented in Annual Reports* (December 2021)
- *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014)
- *Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA* (October 2022)
- *Field Alert Report Submission: Questions and Answers* (July 2021)

- *SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)
- *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (September 1997)
- *SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)

Draft Guidance for Industry⁴³

- *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021)
- *Postapproval Changes to Drug Substances* (September 2018)
- *SUPAC: Manufacturing Equipment Addendum* (December 2014)

ICH Guidance for Industry

- *Q10 Pharmaceutical Quality System* (April 2009)
- *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021)

D. Objective 4: Integrity of Product Quality Data

Summary: Audit manufacturing controls, test results, and the related raw data for starting materials, in-process materials, and batches of the subject drug. Ensure that the test and production data are authentic, computed correctly, accurate, and documented per CGMP and that they support the associated decisions by the firm, application submissions, and lifecycle changes.

This section emphasizes the importance of data integrity when it has been specifically requested as part of inspectional coverage in the assignment. Additionally, at the discretion of the lead investigator, data integrity coverage may be added when problems are found. Sufficient coverage should be afforded to confirm the integrity of data relating to process performance and product quality.

During routine production, firms generate a substantial amount of manufacturing and laboratory data. Analysis of these data and evaluation of analytical methods ensures that firms are capable of consistently maintaining process control, meeting quality specifications, and reliably producing product of intended quality. Complete, consistent, and accurate data should be attributable, legible,

⁴³ When final, these guidances will represent the FDA's current thinking on these topics.

contemporaneously recorded, original or a true copy, and accurate (ALCOA).⁴⁴ Analysis of product quality data (e.g., release and stability data) also ensures that the quality unit adequately responds to unexpected or aberrant results in a timely manner so as to prevent poor quality drug products from reaching the marketplace.

If a pattern of data reliability issues is identified during the inspection, 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 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.⁴⁵

Inspection Coverage

- Assess the firm's ability to effectively manage hard copy (paper), computerized, and hybrid data systems by having user access control mechanisms and verifiable audit trails, where appropriate, for collection, reporting, and archiving of information for the subject drug.
 - Determine whether data are calculated and reported using reliable and verifiable mechanisms, interpreted using sound scientific rationale, and maintained using validated systems.
 - Determine if there were data not reported in the submission, supplement, or annual report that should have been.
 - Evaluate whether there were inaccurate, misleading, manipulated, or incomplete data in CGMP documents and submissions.
- Evaluate representative raw data relating to process performance and product quality, including the raw data from the in-process, release, and stability testing, to determine if there is a pattern of data reliability issues that impact:
 - The quality specifications of the subject drug.
 - The retest or expiry date or labeled expiration dating.

⁴⁴ These characteristics are important to ensuring data integrity and are addressed throughout the CGMP regulations for drug products. For *attributable*, see 21 CFR 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for *legible*, see 21 CFR 211.180(e) and 212.110(b); for *contemporaneously recorded* (at the time of performance), see 21 CFR 211.100(b) and 211.160(a); for *original or a true copy*, see 21 CFR 211.180 and 211.194(a); and for *accurate*, see 21 CFR 211.22(a), 211.68, 211.188, and 212.60(g).

⁴⁵ Contact information and procedures for OC's Office of Manufacturing Quality are on the AIP website at <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/application-integrity-policy>. See also 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>.

- The analytical methods employed as part of the approved control strategy (e.g., methods do not conform to those approved in the application).⁴⁶

(1) Related Resources

Guidance for Industry

- *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015)
- *Data Integrity and Compliance With Drug CGMP: Questions and Answers* (December 2018)
- *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* (October 2006)

Other FDA Resources

- Compliance program 7346.832—*Preapproval Inspections*, III.1.B(3) Data Integrity Audit (October 2022)
- *Guide to Inspection of Microbiological Pharmaceutical Quality Control Laboratories* (July 1993)
- *Guide to Inspection of Pharmaceutical Quality Control Laboratories* (July 1993)

3. Inspection Reporting

The inspection team performs the inspection following this compliance program and provides coverage in the areas of concern.

A. Issuance of Form FDA 483

Consistent with instructions in the IOM, use Form FDA 483 to communicate reportable observations and CGMP deficiencies pertaining to the subject drug.

Refer to Part V—Regulatory/Administrative Strategy—for a list of issues that may result in a 483 observation.

If the postapproval inspection is concurrent with or expanded to CGMP surveillance, organize Form FDA 483 according to compliance program 7356.002 and the IOM.

B. Completion and Assessment of the Establishment Inspection Report

The inspection team prepares a narrative EIR per instructions in the IOM (chapter 5). In all cases, ORA and CDER (OPMA, Office of Manufacturing Quality (OMQ), or both as described in Part V) collaboratively evaluate the inspection team's report within the context of the application and communicate relevant findings or concerns to the IQA team.

⁴⁶ FDA expects the quality unit to control and approve changes made to these methods and, based on the significance of the change in the method, communicate those changes to FDA.

For postapproval inspections with significant deficiencies, CDER (OPMA, OMQ, or both as described in Part V) evaluates the inspection team's findings and the firm's response and makes a final recommendation on the adequacy of the firm's response for the covered application and/or the facility. CDER (OPMA or OMQ as appropriate) communicates the final recommendation (concurrence/nonconcurrence) to ORA.

4. Sample Collection or Sample Submission Requests

Investigators should not routinely collect samples during the postapproval inspection. Samples of potentially defective subject drugs may be collected to constitute persuasive evidence that significant CGMP problems exist. Physical samples may be an integral part of a CGMP inspection where control deficiencies are observed. Physical samples should be correlated with observed control deficiencies. Contact a program coordinator in the ORS Office of Medical Products, Tobacco, and Specialty Laboratory Operations (ORSOMPSLOProgramCoordinators@fda.hhs.gov) for guidance on the types of samples to be collected (in-process or drug product) and for the appropriate analytical servicing laboratory. Documentary samples may be submitted when the documentation illustrates the deficiencies better than a physical sample. ORA divisions may elect to collect, but not analyze, physical samples, or to collect documentary samples to document CGMP deficiencies. Physical sample analysis is not necessary to document CGMP deficiencies. For sampling guidance, refer to IOM chapter 4—Sampling.

If an official sample is collected at an establishment, use the PACs on the assignment to report sample collection/analysis time.

PART IV—ANALYTICAL

Contact ORS' Office of Medical Products, Tobacco, and Specialty Laboratory Operations (ORSOMPSLOProgramCoordinators@fda.hhs.gov) for the analytical servicing laboratories for chemical and microbiological testing. When contacting ORS for analytical servicing laboratories, provide the product description, lots to be tested, analyses to be performed, and reason for the sample collection.

The analytical servicing laboratory uploads completed analytical worksheets for the product samples analyzed to CMS and submits the original worksheet package to the ORA home district office of the manufacturing facility.

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

PART V—REGULATORY / ADMINISTRATIVE STRATEGY

ORA inspects the establishment named in an application and provides an initial recommendation on its acceptability. If there are significant issues that would adversely impact the establishment's ability to perform its designated functions as described in the application, the lead investigator documents the nature and scope of significant deviations and observations found during the postapproval inspection for the subject drug.

1. Significant Issues

Examples of significant issues for the subject drug include but are not limited to the following⁴⁷:

1. Lack of or inadequate process validation (e.g., unsuitable equipment, inadequate process performance qualification, unreliable state of control) to support distribution of the subject drug.
2. Lack of or inadequate validation of test methods for raw materials, in-process materials, or the subject drug.
3. Release or distribution of batches that deviated from the site's established procedures as well as the controls in the approved application (e.g., reprocessing or rework operations, process controls, test methods, raw material, in-process material specifications, and subject drug specifications).
4. Failure to investigate and resolve quality problems (e.g., manufacturing issues, including stability failures, OOS or OOT results, consumer complaints) for distributed batches.
5. Failure to investigate and document the root cause of deviations, failure to initiate CAPAs to correct deviations and prevent them from recurring, and failure to assess the impact on product quality.
6. Failure of the quality unit to adequately review, assess, and approve changes relevant to the subject drug.
7. A finding of data integrity problems.⁴⁸
8. Failure to meet application commitments by the agreed-upon timeline without a reasonable justification and with no or inadequate communication to FDA.
9. Failure to report or inadequate reporting of changes made to the subject drug, as applicable (e.g., changes made to approved ECs).

⁴⁷ In general, issues 1 to 7 are considered typical examples of CGMP deficiencies, whereas issues 8 and 9 are typical examples of application-related issues. Issues related to drugs that have already been distributed are considered more significant for potential negative impact to patients or consumers.

⁴⁸ Findings related to raw data integrity or falsification of data generated at the manufacturing site and used in support of product quality decisions relevant to the subject drug should be considered for a systemic CGMP impact on current operations (e.g., across all manufacturing operations or across all manufactured products as applicable) at the establishment.

If significant issues are identified during the postapproval inspection, the lead ORA investigator, as indicated in Part II.3.E of this compliance program, should consider expanding the scope of the inspection to include compliance program 7356.002 coverage.

2. Coordination for Regulatory/Administrative Follow-Up Actions to Inspection Findings

Inspection findings that demonstrate that the manufacturing process is not operating under a state of control may be used as evidence for taking appropriate advisory, administrative, or judicial actions.

The initial classification of the inspection should be based on the ORA division's assessment of the seriousness of the inspectional issues observed.

The endorsement of the inspection report will point out the actions by the firm that have been or will be taken and the timeline for the actions. All deficiencies noted in inspections under this compliance program must be addressed by stating the firm's corrective actions, accomplished or projected, for each deficiency as established in the discussion with the firm's management at the close of the inspection.

If an inspection report documents significant deficiencies for the subject drug or finds one or more systems at the establishment that are not in a state of control with or without the expanded inspection coverage under compliance program 7356.002, consider an initial OAI classification for impacted PACs.

A. Issues That Are Considered Significant for PAC 56843

The issues that are considered significant for PAC 56843 may impact other drug products or APIs besides the subject drug under inspection. OMQ and OPMA, when appropriate (i.e., specifically for the subject drug), will collaborate on the determination of combined actions (e.g., regulatory, advisory, enforcement). OMQ, ORA, and OPMA will subsequently collaborate on related communication with the firm or applicant, as appropriate.

When the postapproval inspection identifies the presence of significant CGMP deficiencies for the subject drug, as described in Part V of this compliance program, or if the postapproval inspection is combined with surveillance inspection coverage and there are significant deficiencies identified as described in Part V—Regulatory/Administrative Strategy of compliance program 7356.002, the inspection should result in an initial OAI classification recommendation to OMQ.

In these instances, OMQ will act as the lead office tasked with completing the final assessment, providing a compliance recommendation, and issuing the FMD-145 letter to the firm. To support OMQ's efforts, OPMA may assign a point of contact to actively assist in the review of the inspection report and the firm's responses to the 483 observations. When appropriate, OMQ can also initiate a product-specific consult to OPMA (such as to solicit subject matter expert opinion on the impact of identified microorganisms or other complex manufacturing process or facility issues). When necessary, OPMA will reach out to appropriate OPQ suboffices in response to the OMQ consult.

Regulatory, advisory, or enforcement actions may include one or more of the following:

- Hold a regulatory meeting (or meetings) with the manufacturer.

- Issue a warning letter (or other advisory notice).
- Pursue an import alert (for foreign manufacturers).
- Order a cease distribution or product recall or recommend a product recall.⁴⁹
- Pursue product seizure.
- Pursue establishment injunction.
- Suspend product approval.
- Withdraw or revoke product approval (following the opportunity for a hearing or an opportunity to demonstrate compliance).
- Withhold the approval of pending applications and application supplements requiring an evaluation of the establishment.
- Invoke FDA's Application Integrity Policy.
- Pursue prosecution.
- Pursue the imposition of civil money penalties.
- Initiate an administrative detention of the subject drug, per 21 CFR 1.980.

The postapproval inspection may find no significant CGMP deficiencies but may identify application-related issues with an initial OAI classification for PAC 56843 requiring CDER's follow-up.⁵⁰ In these instances, OPMA will lead the assessment of the inspection outcomes on the subject drug application, coordinate with the IQA team for subsequent follow-up actions or communications with the applicant or the facility as necessary, and act as the lead office tasked with completing the final assessment and issuing the FMD-145 letter to the firm. To support OPMA's efforts, OMQ may assign a point of contact to actively assist in the review of the inspection report as well as other relevant inspectional documents. When appropriate, OPMA can also initiate a compliance-specific consult to OMQ. When necessary, OMQ will reach out to appropriate OC suboffices in response to the OPMA consult. OPQ can ask the applicant, site, and related programs, as needed, to undertake follow-up actions regarding subject drug-related issues. Follow-up actions may include, but are not limited to:

- Requesting that an applicant submit a supplement to modify ECs named in the application.
- Notifying the applicant that the reporting categories previously approved in the application related to the facility subject to the postapproval inspection will revert to reporting categories consistent with the risk-based paradigm in the regulations and as recommended in guidance until adequate corrections have been verified.

Lack of follow-up on these application-focused corrections may also impact pending applications.

⁴⁹ For a cease distribution or product recall of a controlled substance, refer to section 569D of the FD&C Act.

⁵⁰ Examples of application-related issues include an inappropriate change reporting category, failure to meet application commitments relevant to drug quality, failure to submit annual reports, and concerns about the PQS that impact an approved PLCM document or suggest that additional ECs should be included in the application.

OPMA works with other offices (e.g., Office of Combination Products (OCP) and Office of the Chief Counsel (OCC), Office of Generic Drugs (OGD), OMQ) to determine the appropriate administrative actions, which may include but are not limited to the following:

- FDA-initiated request to the applicant to update an existing approved application.
- Withdrawal of approval status of the application (NDA and ANDA) or its suspension under section 505(e) of the FD&C Act (see also 21 CFR 314.150(b), 314.151, and 314.153).

After the final classification of the inspection has been completed, OQS updates the surveillance risk model, when appropriate, with the information gained from the inspection.

B. Issues That Are Not Considered Significant for PAC 56843

If the facility inspection indicates an NAI or VAI classification and no further action is recommended, ORA issues an FMD-145 letter within the predefined timeline based on the date of the inspection closing.⁵¹ OPQ suboffices (e.g., OPMA) may assist ORA divisions as requested.

⁵¹ See FMD-145—Release of the Establishment Inspection Report (EIR).

PART VI—REFERENCES, ATTACHMENT, PROGRAM CONTACTS, AND ACRONYMS**1. References****A. Code of Federal Regulations, Title 21**

<https://www.ecfr.gov/current/title-21>

21 CFR part 1

21 CFR part 210

21 CFR part 211

21 CFR part 212

21 CFR part 310

21 CFR part 314

B. Compliance Programs

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

7346.832—*Preapproval Inspections*

7356.002—*Drug Manufacturing Inspections*

7356.002A—*Sterile Drug Process Inspections*

7356.002C—*Radioactive Drugs*

7356.002F—*Active Pharmaceutical Ingredients*

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

7356.021—*Drug Quality Reporting System (DQRS) (MedWatch Reports) NDA Field Alert Reporting (FARs)*

C. Compliance Policy Guide

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

CPG Sec. 120.100 *Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities*

D. FDA Guidances

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

(1) Guidance for Industry

Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015)

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

Changes to an Approved NDA or ANDA (April 2004)

Changes to an Approved NDA or ANDA: Questions and Answers (January 2001)

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

CMC Postapproval Manufacturing Changes for Specified Biological Products to be Documented in Annual Reports (December 2021)

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

Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA (October 2022)

Control of Nitrosamine Impurities in Human Drugs, Rev. 1 (February 2021)

Current Good Manufacturing Practice Requirements for Combination Products (January 2017)

Data Integrity and Compliance With Drug CGMP: Questions and Answers (December 2018)

Field Alert Report Submission: Questions and Answers (July 2021)

Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (October 2006)

Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency: Questions and Answers (May 2021)

Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs (April 2012)

PET Drugs—Current Good Manufacturing Practice (CGMP) (December 2009)

PET Drugs—Current Good Manufacturing Practice (CGMP), Small Entity Compliance Guide (August 2011)

Process Validation: General Principles and Practices (January 2011)

Quality Systems Approach to Pharmaceutical CGMP Regulations (September 2006)

Questions and Answers on Current Good Manufacturing Practices for Drugs (March 2018)

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

Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice (October 2004)

SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995)

SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (September 1997)

SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (May 1997)

Draft guidance⁵²

Benefit-Risk Considerations for Product Quality Assessments (May 2022)

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

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

Postapproval Changes to Drug Substances (September 2018)

SUPAC: Manufacturing Equipment Addendum (December 2014)

(2) ICH Guidance for Industry

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

Q8(R2) Pharmaceutical Development (November 2009)

Q9(R1) Quality Risk Management, Draft (June 2022)

Q10 Pharmaceutical Quality System (April 2009)

Q11 Development and Manufacture of Drug Substances (November 2012)

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

E. Other Procedures and References

Application Integrity Policy, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/application-integrity-policy>

FMD-145—Release of the Establishment Inspection Report (EIR) (July 2019), <https://www.fda.gov/media/83055/download>

⁵² When final, these guidances will represent the FDA's current thinking on these topics.

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

- *Pharmaceutical Quality Control Laboratories* (July 1993)
- *Microbiological Pharmaceutical Quality Control Laboratories* (July 1993)

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>

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>

Points to Consider for Internal Reviews and Corrective Action Operating Plans (June 1991), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/application-integrity-policy/points-consider-internal-reviews-and-corrective-action-operating-plans-june-1991-food-and-drug>

Regulatory Procedures Manual (July 2021), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual>

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>

United States Pharmacopeia (USP), <https://www.uspnf.com>

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

2. Attachment

Attachment A: Remote Regulatory Assessments

3. Program Contacts

A. 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

Staff Director

ORSOMPSLOProgramCoordinators@fda.hhs.gov**B. 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 program, send an email to the following address and it will be handled as a top priority:

OPQPolicy@fda.hhs.govProduct-Specific Inspection-Related Questions:

For questions about a product-specific postapproval inspection under this program, contact the OPMA Postapproval Program mailbox:

CDERPostApprovalProgram@fda.hhs.govOffice 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**4. Acronyms**

ALCOA	attributable, legible, contemporaneously recorded, original or a true copy, and accurate	CDER	Center for Drug Evaluation and Research
ANDA	abbreviated new drug application	CGMP	current good manufacturing practice
API	active pharmaceutical ingredient	CMC	chemistry, manufacturing, and controls
CAPA	corrective action and preventive action	CMS	Compliance Management Services
CBE	changes being effected	Cpk	process capability index

DMF	drug master file	OPMA	Office of Pharmaceutical Manufacturing Assessment
DOE	design of experiment	OPQ	Office of Pharmaceutical Quality
EC	established condition	OPQO	Office of Pharmaceutical Quality Operations
eDRLS	Electronic Drug Registration and Listing System	OQS	Office of Quality Surveillance
EIR	establishment inspection report	ORA	Office of Regulatory Affairs
FAR	field alert report	ORA PAM	ORA preapproval program manager
FD&C Act	Federal Food, Drug, and Cosmetic Act	ORADSS	Online Reporting Analysis Decision Support System
ICH	International Council for Harmonisation	ORS	Office of Regulatory Science
IOM	Investigations Operations Manual	PAC	product/assignment code
IQA	integrated quality assessment	PACMP	postapproval change management protocol
MRA	mutual recognition agreement	PAI	preapproval inspection
NAI	No Action Indicated	PET	positron emission tomography
NDA	new drug application	PLCM	product lifecycle management
OAI	Official Action Indicated	pOAI	potential Official Action Indicated
OC	Office of Compliance	Ppk	process performance index
OCC	Office of the Chief Counsel	PPQ	process performance qualification
OCP	Office of Combination Products	PQR	product quality review
OGD	Office of Generic Drugs	PQS	pharmaceutical quality system
OMPTO	Office of Medical Products and Tobacco Operations	RIE	remote interactive evaluation
OMQ	Office of Manufacturing Quality	RRA	remote regulatory assessments
OOS	out-of-specification	SUPAC	Scale-Up and Postapproval Changes
OOT	out-of-trend	VAI	Voluntary Action Indicated

PART VII—OVERVIEW OF CDER-ORA RESPONSIBILITIES

CDER and ORA redefined their roles and responsibilities regarding application assessments and inspections of human drugs facilities under the ConOps agreement *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. Postapproval facility inspections are led by ORA with CDER participation. The roles and responsibilities for postapproval inspections as laid out in ConOps are subject to this compliance program.

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 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 postapproval inspection to support preparation and assessment of product-specific inspection coverage.² The use of 704(a)(4) authority does not prevent an FDA investigator from requesting records or other information on inspection.

2. Remote Interactive Evaluation (Voluntary RRA)

A remote interactive evaluation (RIE) is an evaluation of a firm's compliance with regulations

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*.

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

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 postapproval inspection to evaluate marketed drug products manufactured under approved new drug applications or abbreviated new drug applications or their associated active pharmaceutical ingredients. 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 Emergency*.