CHAPTER 56 – Drug Quality Assurance

SUBJECT: Active Pharmaceutical Ingredient Process Inspection REVISION: Revised to add elements of the International Council for Harmonisation (ICH) guidances for industry *Q9(R1) Quality Risk Management* (May 2023), *Q10 Pharmaceutical Quality System* (April 2009), and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021) and control of hazardous impurities.[1]	IMPLEMENTATION DATE: 09/02/2025

DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
Industry codes 54, 56, and 60-66 inclusive	Domestic and Foreign Inspections: • 56002F (Full Inspection) • 56002L (Abbreviated Inspection) Related Product/Assignment Codes: • 56002 & H (Drug Process Inspections (DPIs)) • 56002C & K (DPIs for Radioactive Drugs)

FIELD REPORTING REQUIREMENTS:

This compliance program[2] covers current good manufacturing practice (CGMP) inspections[3] of active pharmaceutical ingredient (API) facilities[4] to ensure that APIs comply with section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[5] This includes procedures for evaluating compliance with CGMP requirements and providing comprehensive regulatory coverage of all aspects of production and distribution of APIs.

Investigators will create establishment inspection reports (EIRs) and file them electronically using eNSpect or a replacement system that both the Office of Inspections and Investigations (OII) and the Center for Drug Evaluation and Research (CDER) can access. For API inspections that are classified

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

[2] Compliance programs are available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs.

[3] In this compliance program, CGMP inspections include surveillance and for-cause inspections.

[4] This compliance program uses the terms *establishment*, *site*, *firm*, and *facility* interchangeably to cover entities subject to FDA drug manufacturing regulations and statutory authority.

[5] See 21 U.S.C. 351(a)(2)(B).

as official action indicated (OAI) because of CGMP deficiencies as they apply to APIs, CDER will submit advisory, administrative, or judicial action recommendations in the Compliance Management System per the *Regulatory Procedures Manual*.

Investigators should report significant issues in eNSpect. These issues can include analytical or inspectional issues or other issues related to the information developed under this program. This includes promptly filing, changing, and deleting OAI notifications.

If Food and Drug Administration (FDA) staff obtain information about inadequate adverse drug experience reporting, unapproved drug issues, or postapproval reporting (e.g., drug application supplements, field alert reports) violations during an inspection, investigators should report this information under separate captions in the EIR per the directions in the applicable compliance programs. Information about these activities should be reported under separate product/assignment codes.

Contents

PART I – BACKGROUND

1. Introduction

This compliance program applies a risk-based inspection strategy for surveillance inspections of API manufacturing facilities. The procedures in this compliance program maximize the use of resources and enable efficient inspection coverage. Inspection depth should be based on appropriate risks associated with a particular firm's operations. These risks can include the firm's compliance history, the technology employed, the purported characteristics of the API, and the intended use of the API in the drug product, if known. This compliance program also provides procedures for coverage of for-cause inspections.

An API is:

> [A]ny component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.[6]

API production processes commonly include a series of operations. Major operations or steps in an API production process may include multistep chemical synthesis and fermentation, purification, crystallization, drying, milling, packing, labeling, and testing. This compliance program applies to all API manufacturing operations at the establishment, including receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, contract testing, storage and distribution of APIs, and related controls.

2. Applicable Statute, Regulations, and Guidances

Under section 510 of the FD&C Act,[7] API manufacturers must register their establishments with FDA and list their APIs in commercial distribution unless exempted under 21 CFR 207.13. Foreign drug manufacturers are also required to register their establishments and list all drugs imported or offered for import into the United States. Refer to 21 CFR 207.25(h) for additional information on establishment registration requirements for foreign drug establishments.

APIs are subject to the adulteration provisions of section 501(a)(2)(B) of the FD&C Act, which requires that all drugs are manufactured in conformance with CGMP requirements. No distinction is made between an API and a drug product in the FD&C Act, and if either fail to comply with CGMP requirements, they will be in violation of the FD&C Act. Although FDA has published CGMP regulations for drug products, FDA has not published CGMP regulations specifically for APIs or drug components. Thus, the term *CGMP requirements* in this document refers to the requirements of the FD&C Act rather than the requirements for drug products in parts 210 and 211 (21 CFR parts 210 and 211).

[6] See 21 CFR 210.3(b)(7).

[7] See 21 U.S.C. 360.

FDA has long recognized that the concepts in the CGMP requirements for drug products in parts 210 and 211 are valid and applicable for API manufacturing. These concepts include: (1) ensuring drug quality by using suitable equipment and employing appropriately qualified and trained personnel; (2) establishing adequate written procedures and controls designed to ensure that manufacturing processes and controls are valid; (3) establishing a system of tests for in-process materials and drug products; and (4) ensuring that drug products are stable for their intended period of use.

FDA expects API manufacturers to: (1) apply CGMP to the API production process beginning with the use of starting materials; and (2) validate critical process steps that affect the quality and purity of the final API. The appropriate level of control is highly dependent on the manufacturing process and increases throughout the process as it proceeds from early steps to final isolation and purification steps. The appropriate level of control depends on the risk or criticality associated with each specific process step.

In 2001, FDA published the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.[8] ICH Q7 represents FDA's current thinking on CGMP for APIs. Thus, API and related manufacturing and testing facilities that follow this guidance will generally be considered in compliance with the statutory CGMP requirement.[9] However, alternative approaches may be used if such approaches satisfy the requirements of section 501(a)(2)(B) of the FD&C Act and ensure that the API meets its purported purity, identity, and quality characteristics.

ICH Q7 provides guidance to industry on the extent and application of CGMP for manufacturing APIs under an appropriate quality system. The recommendations in ICH Q7 are also intended to help ensure that APIs meet the quality and purity characteristics that they purport or are represented to possess. Investigators should use ICH Q7 as a guideline for inspecting API manufacturers and related facilities.

As part of FDA's continued efforts to advance the Pharmaceutical Quality for the 21st Century initiative, FDA is pursuing strategies to ensure the implementation of an effective pharmaceutical quality system as described in the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009). In addition, FDA published the ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023) to provide principles and examples of tools for quality risk management that can be applied to different aspects throughout a product's lifecycle to ensure pharmaceutical quality. To facilitate the management of postapproval chemistry, manufacturing, and controls changes in a more predictable and efficient manner, FDA published the ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and its *Annexes* (May 2021) and the draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021).[10] Knowledge management, change management, and quality risk management principles should be applied to API manufacturing operations holistically to help ensure API quality. These principles are described in the guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006) in addition to ICH Q9(R1), Q10, and Q12.

[8] ICH Q7 Revision 1 was published in September 2016.

[9] See the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Questions and Answers* (April 2018).

[10] When final, this guidance will represent FDA's current thinking on this topic.

To enhance FDA's regulation of API manufacturing and quality, FDA may use additional information sources to inform its regulatory oversight. This may include the following: (1) other inspections conducted by FDA (e.g., preapproval and postapproval inspections); (2) existing inspection reports requested from trusted foreign regulatory partners through mutual recognition agreements and other confidentiality agreements;[11] and (3) remote regulatory assessments,[12] including (a) records or other information requested directly from facilities and other inspected entities under section 704(a)(4) of the FD&C Act[13] and (b) remote interactive evaluations conducted where appropriate.

3. Scope of APIs Covered by This Program

This compliance program applies to the manufacture of APIs for use in human drug products, including:

- Small molecule APIs and critical intermediates manufactured by chemical synthesis
- Polypeptides consisting of up to 40 amino acids that are manufactured by chemical synthesis or fermentation
- Antibiotics and other small molecule APIs produced by microbial fermentation

This compliance program does not cover APIs for blood, vaccines, allergenics, tissues, and cellular and gene therapies.[14] These products are regulated by the Center for Biologics Evaluation and Research. CGMP inspections of APIs that are *proteins*[15] are conducted using compliance program 7356.002M—*Surveillance Inspections of Protein Drug Substance Manufacturers*. Examples of biological products that contain APIs that are proteins include, but are not limited to:

- Enzymes

[11] For existing FDA mutual recognition agreements with the European Union, Switzerland, 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-agreements-mra.

[12] See the draft guidance for industry *Conducting Remote Regulatory Assessments Questions and Answers* (January 2024). When final, this guidance will represent FDA's current thinking on this topic.

[13] See 21 U.S.C. 374(a)(4).

[14] The term *drug substance* is used for APIs in biological products.

[15] See the definition of *protein* in 21 CFR 600.3(h)(6). *Proteins* are *biological products* as defined by and licensed under section 351 of the Public Health Service Act.

- Monoclonal antibodies
- Antibody-drug conjugates
- Fusion proteins (e.g., antibody Fc region-containing fusion proteins).
- Growth factors
- Cytokines (e.g., interleukins, interferons, tumor necrosis factors)
- Botulinum toxins
- Insulin and insulin analogues
- Synthetically derived proteins

This compliance program applies to the manufacture of APIs intended to be sterile only up to the point immediately before the API is rendered sterile. However, neither this compliance program nor ICH Q7 provide guidance on the sterilization and aseptic processing for sterile APIs. Investigators should use compliance program 7356.002A—*Sterile Drug Process Inspections* and the guidance for industry on aseptic processing, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (September 2004), when inspecting the sterile processing of APIs that are purported to be sterile (including for compounding sterile preparations).

Bulk finished products are manufactured similarly to APIs, but they do not undergo further processing or compounding after their synthesis, fermentation, or extraction and are instead repackaged into market containers. Bulk finished products are subject to the requirements of parts 210 and 211. The synthesis and fermentation processes that result in such APIs are covered by this program rather than the program for dosage forms (i.e., compliance program 7356.002—*Drug Manufacturing Inspections*).

4. Definitions

Active Pharmaceutical Ingredient: "[A]ny component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."[16]

The term drug substance has also been used by FDA and industry to refer to APIs.

API Production Process: A related series of operations which result in the preparation of an active pharmaceutical ingredient. Major operations or steps in an API production process may include multistep chemical synthesis and fermentation, purification, crystallization, drying, milling, packing, labeling, and testing.

API Starting Material: A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API

[16] See § 210.3(b)(7).

starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.

Bulk Finished Product: A drug material that is manufactured similarly to an API but does not undergo further processing or compounding after its synthesis, fermentation, or extraction and is instead repackaged into market containers.

Intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: This compliance program only addresses those intermediates produced after the point that a facility has defined as the point at which the production of the API begins.)

PART II – IMPLEMENTATION

1. Objective

The primary objective of this compliance program is to provide comprehensive CGMP inspectional coverage of API manufacturing establishments. This is done through system-based inspections that represent all profile classes (i.e., types of API manufacturing processes) and determine whether a manufacturer is operating in a state of control. An API manufacturer is operating in a state of control when it employs conditions and practices that ensure compliance with section 501(a)(2)(B) of the FD&C Act. A firm that is in a state of control produces APIs that have an adequate level of assurance of quality, identity, and purity.

A firm is not in a sufficient state of control if any system is significantly noncompliant with CGMP requirements such that the quality, identity, and purity of the API cannot be adequately ensured. Documented CGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control. See Part V - Regulatory/Administrative Strategy, for a discussion of compliance actions based on inspection findings that demonstrate that a system or multiple systems are not in a state of control.

Profile classes generalize inspectional coverage from a small number of specific APIs to all APIs in that class. This compliance program uses a systems-based approach to further generalize inspectional coverage from a small number of profile classes to an overall evaluation of the firm. This allows preapproval inspections to focus on the specific issues related to a given drug application and improves the assessment process by providing timely and efficient support for drug application decisions.

Investigators should use this compliance program's system definitions and organization when inspecting API manufacturers and reporting the results. Focusing on systems, rather than just profile classes, increases the efficiency of inspections, because the systems are often applicable to multiple profile classes. An inspection under this program is profileable and will result in a determination of acceptability or nonacceptability for all API profile classes specified in this compliance program. Inspection coverage should represent all of the API profile classes that are manufactured by the firm.

The other objectives of this compliance program include:

- Determining whether inspected establishments are operating in compliance with applicable CGMP requirements to aid in FDA's enforcement of the FD&C Act.

- Initiating appropriate action against manufacturers that are found to be out of compliance.

- Obtaining information that may affect other drug manufacturing or compounding operations (e.g., sterilization, drug product manufacturing, drug product compounding).

- Providing guidance to manufacturers during inspections to improve compliance with CGMP requirements, as applicable.

2. Program Management Instructions

A. Selecting Sites

CDER uses a risk-based site selection model to identify API firms for OII's routine surveillance inspections. CDER and OII maintain drug profiles per Chapter 5 of the *Investigations Operations Manual* (IOM).[17]

Unless specifically directed by CDER, OII is responsible for determining the depth of inspectional coverage for each API firm using this compliance program's instructions. CGMP inspectional coverage under this program will be sufficient to assess the state of compliance for each firm.

B. Selecting Investigators

Inspections of API manufacturers should be conducted by experienced investigators with sufficient education and training related to the type of API production process or processes conducted by the API manufacturer (e.g., fermentation, chemical synthesis).[18] Chemists and microbiologists should be considered for inclusion on API inspection teams, as appropriate, particularly for evaluating laboratory operations (e.g., analytical methods evaluation, analytical data, laboratory procedures, instrumentation) and assessing analytical methods that are used to establish impurity profiles, fermentation manufacturing processes, and complex multistep processes for chemical synthesis.

Investigators conducting API inspections must understand the basic differences between the processes used to produce APIs and the processes used to produce finished dosage forms. APIs are usually produced by chemical synthesis or by cell culture and extraction. Thus, API production typically involves significant changes to the starting materials or intermediates by various chemical, physical, and biological processing steps. Generally, the ultimate objective in API production is to achieve a pure compound of certain identity. In contrast, the ultimate objective of finished dosage form manufacturing is generally to achieve the uniform distribution of an API across dosing units to deliver a precise amount of API.

C. Selecting Inspection Types

There are two basic types of CGMP inspections: surveillance and for-cause. Surveillance inspections are conducted on a routine basis to satisfy FDA's responsibilities to inspect drug manufacturing facilities. For-cause inspections are conducted in response to violative surveillance inspections and when a need arises to inspect a facility in response to specific events or information.

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

[18] See compliance program 7356.002M for additional inspection guidance on fermentation.

For-cause inspections include: (1) follow-up CGMP compliance inspections to verify corrective actions after a regulatory action has been taken; and (2) CGMP inspections in response to specific events or information (e.g., field alert reports, biological product defect reports, industry complaints, recalls, other indicators of defective products) that bring the compliance or quality of a manufacturing practice, facility, process, or API into question.

Follow-up CGMP compliance inspections provide focused coverage, including the areas of concern, the proposed corrective action plan for affected operations, any implemented corrective actions, and/or the deficiencies noted on Form FDA 483–Inspectional Observations for a previous inspection. System coverage can be added on a case-by-case basis. Follow-up CGMP compliance inspections to a warning letter or other significant regulatory actions are also considered for-cause inspections and, as a result, the related for-cause assignments can request either full systems coverage or individual system coverage. In addition, coverage can be added on a case-by-case basis, at OII's discretion, before or during the inspection.

Other for-cause inspections (e.g., inspections due to industry complaints or other indicators of defective APIs) may be initiated, but these inspections can be expanded to include CGMP coverage for the purpose of updating the firm's overall compliance status.

D. Selecting Systems

This is the general scheme of systems for inspecting API manufacturers:

1. **Quality System** ensures overall compliance with CGMP requirements and internal procedures and specifications. A robust quality system relies on documentation and strong senior management oversight of CGMP operations and quality-related matters, supports and facilitates the activities conducted under all of the six systems, monitors its effectiveness, and ensures a commitment to an established quality policy.[19]

2. **Facilities and Equipment System** includes activities which provide an appropriate physical environment and equipment used in the production of APIs.

3. **Materials System** includes measures and activities to control starting materials, intermediates, and containers. It includes validation of computerized and inventory control processes, storage, and distribution controls.

4. **Production System** includes measures and activities to control the manufacture of APIs, including in-process sampling, testing, and process validation.

[19] *Quality policy* is defined as the overall intentions and direction of an organization related to quality as formally expressed by senior management. See ICH Q10.

5. **Packaging and Labeling System** includes measures and activities that control the packaging and labeling of intermediates and APIs.

6. **Laboratory Control System** includes measures and activities related to laboratory procedures, testing, analytical methods development, analytical methods validation or verification, and the stability program.

Inspectional Section III.1.B has detailed inspection coverage guidance for these systems.

An inspection under this program is defined as audit coverage of two or more systems, including mandatory coverage of the quality system. Inspecting at least two systems (i.e., the quality system and one other system), or more systems if deemed necessary by OII, will provide the basis for an overall inspection classification decision.

Coverage of a system should be sufficiently detailed and specific examples should be selected. Sufficient coverage ensures that the system inspection outcome reflects the system's state of control for every profile class. If a particular representative system is adequate, it should be adequate for all drug profile classes manufactured by the firm. In some circumstances, it may not be possible to generalize certain deficiencies in a system to all API profile classes. If so, the unaffected profile classes may be considered acceptable if they are otherwise acceptable.

If a selected API has a unique processing or control function that is part of a system that was not chosen for coverage, the unique function can be covered for that API. However, the system for the unique function does not need to be given full coverage. For example, if an API chosen for coverage uses only high purity water in its manufacture, the water purification system can be inspected without giving full inspection coverage to the materials system. Selecting unique functions within a system will be at the discretion of the investigator.

Complete inspection of one system may require follow up of certain aspects of another system to fully document the findings. However, this coverage does not constitute nor require complete coverage of the other system.

E. Selecting APIs

Inspections should cover any APIs referenced in the assignment and, as appropriate, any other representative APIs based on their level of risk. For foreign API firms, investigators should cover only APIs that are marketed or intended to be marketed in the United States.

Investigators should select APIs so that the coverage represents the establishment's overall ability to manufacture in compliance with CGMP requirements. API selection should also be based on the level of risk, including selection of APIs that are:

- Used in approved drug products
- Therapeutically significant
- Difficult to manufacture

- Intended for use in parenteral or modified-release products or in combination products[20]
- Documented as having past compliance problems

However, this does not prevent investigators from selecting less therapeutically significant APIs to evaluate specific APIs (or profile classes) that were not previously given in-depth coverage at the facility. Inspection coverage depth and intensity can be reduced for these APIs unless deficiencies are identified.

When a system is inspected, the inspection of that system generally applies to all API products that use the system. Because API manufacturers are often referenced in multiple drug applications, each inspection should cover an adequate number and type of APIs to cover the selected systems. For example, if an inspection covers the production system for a site making one API by fermentation and another by synthesis, the inspection should include both types of processing in the physical inspection and the records that are sampled during the audit. This strategy, together with the classification of all applicable profile classes after the inspection, will maximize the use of FDA resources and avoid repeated visits to the same manufacturing site to cover different API profile classes.

F. Selecting Profile Classes

Profile class codes[21] or APIs selected for coverage should represent all of the APIs manufactured at the firm. Profile class codes may also be grouped by similarity, such that coverage of one profile class is sufficient to demonstrate the CGMP conditions for another profile class. For example, inspecting a profile class code of CSS[22] could provide surrogate coverage of CSN. Similarly, inspecting a profile class code of CBI could provide surrogate coverage of other profile classes, such as CFN, CFS, and perhaps CEX.

The inspection findings will be used to update all applicable profile classes.[23] Normally, an inspection under this system approach will result in all applicable profile classes being updated. For more information, see Exhibit 5-14 Profiling a Firm's CGMP/QS Compliance Status in the IOM.

[20] Combination products are subject to the CGMP requirements outlined in 21 CFR part 4. See the guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017) and compliance program 7356.000—*Inspections of CDER-led or CDRH-led Combination Products*.

[21] A profile classification scheme is used to categorize APIs by the nature of their processing.

[22] This compliance program applies to the manufacture of sterile APIs only up to the point immediately before the APIs are rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this compliance program. Investigators should use the finished pharmaceuticals regulations (parts 210 and 211) and follow compliance program 7356.002A when inspecting the sterile processing of APIs.

[23] Profile classes are not updated for a preapproval inspection of an API unless the preapproval inspection covers a new profile. See also compliance program 7346.832—*Preapproval Inspections.*

PART III – INSPECTIONAL

1. Operations

Investigators conducting API inspections should understand the general inspection strategy in this compliance program. API firms vary greatly in size, diversity of operations, and quality assurance systems, so investigators should carefully plan their inspection strategy at each firm. See Part III.1.C for the procedures for preparing an inspection strategy.

Investigators should also review the firm's rationale for the point at which API production begins, as described in ICH Q7 and the ICH guidance for industry *Q11 Development and Manufacture of Drug Substances* (November 2012). This point may vary based on the type of process used for the API (e.g., synthesis, fermentation, extraction, purification).

A. Inspection Approaches

Surveillance inspections have two inspection options: a full inspection and an abbreviated inspection. For-cause inspections can provide focused coverage, or they can be expanded to abbreviated or full inspections on a case-by-case basis, at OII's discretion.

(1) Full Inspection Option

The full inspection option is a CGMP inspection that provides a broad and in-depth evaluation of the establishment's conformance with CGMP requirements. A full inspection may change to an abbreviated inspection with concurrence from OII.

During the course of a full inspection, coverage in other systems may be needed to verify quality system activities. The full inspection option should include an inspection of at least four systems, one of which must be the quality system.

A full inspection is appropriate for the following cases:

- For an initial inspection of a newly registered establishment. Inspection coverage should include all the systems that are appropriate for the operations.

- When the establishment has a history of fluctuating into and out of compliance. To determine if the establishment meets this criterion, OII should use all of the information at its disposal. This information can include inspection results, results of sample analyses, complaints, defects, drug quality reports, field alert reports, adverse event reports, and recalls, in addition to any compliance actions resulting from these types of information or from past inspections.

- To evaluate whether important changes have occurred by comparing current operations against the EIR from the last full inspection. The following are typical types of changes that warrant the full inspection option:

- Changes that introduce a new potential for cross-contamination through the type of materials that use the same equipment or the type of processing.

- Use of new technology requiring new expertise, significant equipment changes, or new facilities.

- When OII management or CDER requests this option.

- To follow up on a warning letter or other regulatory actions.

- When, at OII's discretion, a full inspection needs to be conducted based on CGMP findings.

(2) Abbreviated Inspection Option

The abbreviated inspection option is a CGMP inspection that efficiently updates the evaluation of and provides documentation for an establishment's conformance with CGMP requirements. The abbreviated inspection option should include an inspection audit of two to three systems, one of which must be the quality system. OII's division management should ensure that the optional systems are rotated in successive abbreviated inspections. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems.

An abbreviated inspection is appropriate when a full inspection is not warranted. This option involves inspecting the manufacturer to: (1) maintain surveillance over the establishment's manufacturing practices and quality performance; and (2) evaluate whether the establishment is maintaining and improving the CGMP level of assurance for the quality of its APIs. Select the abbreviated inspection option (with OII concurrence) when an establishment has:

- A record of sustained acceptable compliance history
- A strong risk management program
- A lack of significant marketed API quality defects.

An abbreviated inspection may be changed to a full inspection at OII's discretion.

B. System Coverage

This section provides a complete description of each system and the areas for coverage. Investigators should take the firm's specific operating conditions, history of previous coverage, and history of

CGMP compliance into consideration when selecting systems and determining the relative depth of the audit's coverage.

The organization and personnel (including appropriate qualifications and training), employed in any given system, will be evaluated as part of that system's operation. Production, control, or distribution records are required to maintain CGMP compliance, and the records selected for review should be included for inspection audit within the context of each of the systems. Inspection of contract companies should include (1) coverage within the system for which the intermediate, API, or service is contracted; and (2) evaluation of their quality system.

Each of the following system descriptions has a bulleted list of areas. The firm should have written and approved procedures and documentation for each of these areas. Whenever possible, investigators should verify (through observation) if firms are adhering to written procedures. For each system, the areas are not limited to the final API but may also include starting materials and intermediates. All areas under each system should be covered; however, the depth of coverage may vary from the planned inspection strategy depending on inspectional findings.

(1) Quality System

The quality system is assessed in two phases. In phase one, investigators evaluate whether the quality unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance. Additionally, investigators will evaluate if the quality unit has ensured that the procedures and the associated record keeping systems are adequate for their intended use. In phase two, investigators assess the data and identify any quality problems. This phase may link to other major systems for inspectional coverage.

Evaluate each of the areas listed below. If there are additional considerations for the area, they are listed in sub-bullets.

- Quality oversight of contracted operations and material suppliers
  - An effective monitoring strategy has been implemented; incoming material monitoring, life cycle qualification program, quality agreements, and timely communication mechanisms are implemented.

- Management oversight of the development, implementation, monitoring, and continual improvement of the quality system[24]
  - Quality risk management[25] and knowledge management[26] are incorporated (e.g., timely and effective communication, appropriate resource allocation, reviews of process performance and API quality).

[24] See ICH Q10.

[25] See ICH Q9(R1).

[26] Effective knowledge management (e.g., acquiring, analyzing, storing, and disseminating information) supports effective risk management, along with timely risk review, corrective actions and preventive actions, and change management.

- Quality oversight of hazards (e.g., cross-contamination, adulteration, hazardous impurities[27] such as nitrosamines[28] and nitrosating agents)
  - Hazards are documented, identified, evaluated, addressed, communicated, and continually reviewed (as needed) throughout the API's life cycle.
  - Hazardous impurity risks are assessed, and control strategies are implemented to mitigate the risks (e.g., actions to address sources of variability, release testing, reduction or elimination of impurities, cleaning validation); control strategies are reviewed following changes and throughout the API's life cycle.

- Adequate staffing to ensure fulfillment of quality unit duties

- Periodic quality reviews as described in ICH Q7
  - Reviews are complete and conducted at least annually; API quality is reviewed to assess risk and determine the need for changes, such as changes in API specifications, manufacturing, or control procedures; statistical analysis is conducted to identify areas (e.g., trends, patterns, correlations, anomalies) for action and improvement.

- Complaint reviews (quality and medical)
  - Reviews are documented, evaluated, and investigated in a timely manner; corrective action is included when appropriate.

- Discrepancies, failures, and critical deviations related to manufacturing and testing
  - These issues are documented and investigated in a timely manner using scientific evidence to identify the root cause; corrective actions and preventive actions are included, and the effectiveness of the corrective and preventative actions is evaluated; investigations are expanded to include any related APIs or materials.

- Stability failures
  - Investigation is expanded where warranted; disposition is documented; stability data supports the API retest dates and storage conditions.

[27] See the ICH guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023).

[28] See the guidance for industry *Control of Nitrosamine Impurities in Human Drugs* (September 2024).

- Change management for the manufacturing of all APIs
  - Changes are documented (with justification), reviewed by subject matter experts, approved before implementation, and evaluated for effectiveness; changes are revalidated, reverified, and requalified as needed; quality risk management[29] is used to evaluate proposed changes for potential risks (e.g., hazardous impurities) and impact on API quality; changes are reported to FDA by the drug application or drug master file (DMF) holder, as appropriate.

- Reporting of changes for approved drug application products
  - Changes to established conditions are documented and communicated to the drug application holder, as appropriate. This enables reporting that is compliant with relevant regulations[30] and consistent with the product life cycle management document in the drug application or recommendations in relevant guidance.[31]

- Rejects
  - Investigations are expanded when warranted; corrective actions and preventative actions are implemented, when appropriate.

- Quality oversight system for the release or rejection of raw materials

[29] See ICH Q10.

[30] See 21 CFR 314.70 and 314.97.

[31] See the following guidances for industry:

- *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)
- *Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)
- *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)
- *Changes to an Approved NDA or ANDA* (April 2004)
- *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021)
- *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014)

See also ICH Q12, its annexes, and the draft guidance *ICH Q12: Implementation Considerations for FDA-Regulated Products*.

- Batches manufactured since the last inspection to evaluate any rejections or conversions (e.g., from drug to nondrug use) because of processing problems

- Recalls (including any attempt to recover distributed API not meeting its specifications or purported quality)
  - The cause was determined; corrective actions were taken.

- Validation
  - The statuses of validation and revalidation activities (e.g., computer, manufacturing process, laboratory methods) are documented (e.g., reviews and approvals of validation protocols and reports).

- Contemporaneous and complete documentation[32]

- CGMP training and qualification for employees on a continuing basis and with sufficient frequency
  - Training includes coverage of quality functions, risk management, and the specific CGMP operations assigned to individual employees.

- Programs for the ongoing monitoring of process performance and API quality throughout the API's life cycle
  - Significant issues are escalated to senior management.

- Reprocess and rework
  - Evaluation is conducted; approval is documented; impact on validation and stability is assessed.

- Returns and salvages
  - Assessment is conducted; investigation is expanded where warranted; disposition is completed.

[32] See the guidance for industry *Data Integrity and Compliance With Drug CGMP: Questions and Answers* (December 2018).

(2) Facilities and Equipment System

(a) Facilities

Evaluate each of the areas listed below. If there are additional considerations for the area, they are listed in sub-bullets.

- Responsible personnel's oversight of the facility infrastructure and the suitability of manufacturing operations
- Change management system for implementing changes in the facility
- Facility layout, material flow, and personnel flow that prevent cross-contamination, including cross-contamination from processing of nondrug materials
- Complete and comprehensive separation of the manufacturing operations for highly sensitizing agents (e.g., penicillin, beta-lactams, steroids, hormones, and cytotoxics)
- Qualified and appropriately monitored utilities (e.g., steam, gas, compressed air, heating, ventilation, air conditioning)[33]
- Lighting, potable water, washing and toilet facilities, and sewage and refuse disposal
- Cleaning and maintenance that potentially affect API quality
- Sanitation of the facility and use of rodenticides, fungicides, insecticides, and cleaning and sanitizing agents
- Training and qualification of personnel

(b) Equipment

Evaluate each of the areas listed below. If there are additional considerations for the area, they are listed in sub-bullets.

[33] Note that this system includes only those utilities whose output is not intended to be incorporated into the API, such as water used in cooling or heating jacketed vessels.

- Equipment installation
  - Equipment is operational; performance is qualified, when appropriate.

- Adequate equipment design, size, and location

- Controls to prevent contamination, including appropriate design provisions to ensure separation from pesticides, other toxic materials, or nondrug chemicals

- Equipment surfaces that are not reactive, additive, or absorptive in a way that could alter material quality

- Appropriate identification of equipment (e.g., reactors, storage containers) and permanently installed processing lines

- Prevention of contact between substances associated with the operation of equipment (e.g., lubricants, heating fluids, coolants) and starting materials, intermediates, final APIs, and containers

- Cleaning procedures and cleaning validation and sanitization studies to verify that residues, microbial contamination, and, when appropriate, endotoxin contamination are brought below scientifically appropriate levels

- Calibrations that use standards that can be traced to certified standards (e.g., National Institute of Standards and Technology, United States Pharmacopeia (USP))

- Qualification, calibration, and maintenance of storage equipment (e.g., refrigerators, freezers) to ensure that materials (e.g., standards, raw materials, reagents) are stored under appropriate conditions

- Equipment (including computers) qualification, validation, calibration, maintenance, and security

- Control system for implementing changes to equipment

- Documentation of any discrepancies (critical discrepancy investigations are covered under the quality system)

- Training and qualification of personnel

(3) Materials System

Evaluate each of the areas listed below. If there are additional considerations for the area, they are listed in sub-bullets.

- Training and qualification of personnel

- Identification of starting materials and containers

- Storage conditions

- Quarantine of all materials and APIs (including reprocessed materials) until they are tested or examined and released

- Collection of representative samples for testing or examination
  - Appropriate means are used; comparisons are against appropriate specifications.

- A system for auditing and monitoring the suppliers of critical materials (e.g., raw materials, starting materials, intermediates) and containers

- Rejected materials
  - Decisions to keep or reject materials that do not meet acceptance requirements (e.g., starting materials, intermediates, containers) are documented and justified; rejected materials are promptly quarantined and disposed.

- Appropriate retesting or reexamination of starting materials, intermediates, and containers

- First in, first out use of materials and containers

- Suitability of process water used to manufacture APIs, including the water system design, maintenance, validation, and operation, as appropriate

- Suitability of process gas used in the manufacture of APIs (e.g., gas use to sparge a reactor), including the gas system design, maintenance, validation, and operation, as appropriate

- Containers and closures that are not additive, reactive, or absorptive

- Change management system for implementing changes in material handling operations
  - Changes in the supply chain for critical materials and containers are thoroughly evaluated, approved, and documented to ensure that they are unlikely to pose an adverse risk to API quality.

- Qualification, validation, and security of computerized or automated processes

- Distribution records by batch for all materials (e.g., the finished API, intermediates), including records for exported materials

- Documentation of any discrepancies (critical discrepancy investigations are covered under the quality system)

- Risk management program for starting materials, intermediates, and containers
  - Unacceptable hazards (e.g., impurities) are addressed; risks are assessed, as needed, throughout the API's life cycle.

(4) Production System

Evaluate each of the areas listed below. If there are additional considerations for the area, they are listed in sub-bullets.

- Training and qualification of personnel

- Establishment of, adherence to, and documented performance of approved manufacturing procedures

- Controls for critical activities and operations

- Documentation and investigation of critical deviations

- Comparison of actual yields with expected yields at designated steps

- Process validation[34] program that ensures a state of control across the life cycle (i.e., process design, process qualification, and continued process verification stages)

- Establishment of adequate control steps to ensure that APIs are suitable and safe for their intended use
  - For APIs intended to be used in parenteral dosage forms, pyrogenic (e.g., endotoxin) contamination can be reduced or prevented through the use of appropriate water quality, input materials, and process steps.

- Established time limits for completion of phases of production, when appropriate

- Appropriate identification of major equipment used in the production of intermediates and the API

- Justification and consistency of intermediate specifications and API specifications

- Implementation and documentation of process controls, testing, and examinations (e.g., pH, temperature, purity, actual yields, clarity)

- In-process sampling that is conducted using procedures designed to prevent contamination of the sampled material

- Recovery (e.g., from mother liquor or filtrates) of reactants
  - Approved procedures and recovered materials meet specifications that are suitable for their intended use.

[34] See the guidance for industry *Process Validation: General Principles and Practices* (January 2011).

- Recovery of solvents
  - Recovered solvents should be used only in the same step or in an earlier step (if there is sufficient purification) of the same processes from which they were collected.

- Precautions to prevent or minimize the potential for cross-contamination when APIs are micronized on multiuse equipment

- Validation and security of computerized or automated processes

- Ongoing statistical evaluations (e.g., batch control data, periodic capability analysis) to identify processes that exhibit high variability and trigger needed improvements

- Change management system for production changes, including evaluation of the need for additional validation studies

- Master batch production and control records that include instructions and processes of appropriate specificity that enable production operators to reproducibly execute the same manufacturing processes each time the API is produced

- Batch production and control records

- Contemporaneous and complete documentation of batch production

- Documentation of any discrepancies (critical discrepancy investigations are covered under the quality system)

- Establishment of effective control strategies for manufacturing operations that may potentially pose a risk of forming hazardous impurities

(5) Packaging and Labeling System

Evaluate each of the areas listed below. If there are additional considerations for the area, they are listed in sub-bullets.

- Training and qualification of personnel

- Acceptance operations for packaging and labeling materials
- Establishment of, adherence to, and documented performance of approved packaging and labeling procedures
- Change management system for implementing changes in packaging and labeling operations
- Adequate storage for labels and labeling, both approved and returned after issued
- Control of labels with similar sizes, shapes, and colors that are used for different APIs
- Adequate packaging records that include specimens of all labels used
- Control of issuance of labeling, examination of issued labels, and reconciliation of used labels
- Examination of the labeled finished APIs
- Adequate inspection (i.e., proofing) of incoming labeling
- Use of lot numbers and destruction of excess labeling bearing lot or control numbers
- Adequate separation and controls when more than one batch is labeled at a time
- Adequate expiration or retest dates on the label
- Validation of packaging and labeling operations including validation and security of computerized processes
- Documentation of any discrepancies (critical discrepancy investigations are covered under the quality system)

- Repackaged APIs and intermediates
  - The name of and information about the original API or intermediate manufacturer, repacker, and relabeler are provided.

(6) Laboratory Control System

Evaluate each of the areas listed below. If there are additional considerations for the area, they are listed in sub-bullets.

- Training and qualification of personnel
- Adequate staffing for laboratory operations
- Adequate equipment and facility for the intended use
- Calibration and maintenance programs for analytical instruments and equipment
- Validation and security of computerized or automated processes
- Source and purity of reference standards
  - Assays and tests are used to establish equivalency to current official reference standards, as appropriate.
- System suitability tests for chromatographic systems
- Specifications, standards, and representative sampling plans
- Validation or verification of analytical methods, including suitability of microbiological test methods
- Adequate test methods for establishing complete impurity profiles for each API production process[35]

[35] Note that impurity profiles are often process-related.

- Reassessment of impurity profiles after changes that could affect the impurity profile (e.g., new sources of raw materials or reagents)

- Change management strategy for hazardous impurities if any hazardous impurities have been identified: (1) in any starting material, intermediate, container, or the API; or (2) as a degradant during the API's life cycle

- Change management system for implementing changes in laboratory operations

- Required testing of the correct samples using the approved or filed methods or equivalent methods

- Documentation of any discrepancies (critical discrepancy investigations are covered under the quality system)

- Complete analytical records from all tests and summaries of results

- Contemporaneous and complete laboratory records

- Quality and retention of raw data (e.g., chromatograms, spectra)

- Correlation of result summaries to raw data; presence and disposition of unused data

- Adherence to an adequate out of specification procedure that includes timely completion of investigations

- Adequate reserve samples and documented examination of reserve samples

- Stability testing program, including demonstration that the analytical methods are stability-indicating

C. Preparing the Inspection Strategy

These procedures are in addition to those in the IOM.

1. Select two or more systems for inspection coverage, as appropriate (see Part III.1.A).

2. If APIs are not specified in the assignment, select significant APIs for inspection coverage. APIs are considered significant based on risk. Significant APIs include: (1) APIs that broadly use all of the systems in the firm or use special manufacturing features (e.g., complex chemical synthesis); and (2) APIs that are highly sensitizing materials, infectious materials, or new chemical entities made under approved drug applications. Review the firm's inspection history, compliance history, DMF, or drug application files.

3. If CDER or OII request a CDER staff member to be a member of the inspection team, the lead investigator should brief them on the intended inspection strategy and explain their supporting role and responsibilities for the inspection. The lead investigator should consult with OPQ assessors on any specific drug application chemistry, manufacturing, or control issues (whether premarket or postmarket) that will be covered during the inspection.

4. Review the impurity profile for each API production process that will be covered during the inspection. If an application or DMF was submitted, compare the firm's impurity profiles to the impurity profiles submitted.[36,37]

5. For the APIs that will be inspected, verify conformity to any compendial monographs, as appropriate.

6. Before or during the inspection, determine if the firm has made process changes by comparing current operations against the EIR for the previous inspection. Also compare the current operations with those described in the DMF or the drug application to determine whether the firm is complying with the postapproval chemistry, manufacturing, and controls commitments that they made to FDA.[38] The following are examples of changes that would warrant extensive coverage during the inspection:

    a. API production process changes or product-type line changes that include processing of several APIs of varying toxicity in common equipment and/or facilities. These changes could introduce new potential cross-contamination.

[36] Investigators and chemists should be particularly familiar with USP General Chapter <1086> *Impurities in Drug Substances and Drug Products* and the ICH guidances for industry *Q3A Impurities in New Drug Substances*, Revision 2 (June 2008), *Q3C(R8) Impurities: Guidance for Residual Solvents* (December 2021), and *Q3D(R2) Elemental Impurities* (September 2022)

[37] See the guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (August 2023).

[38] See also compliance program 7346.832—*Preapproval Inspections* for conducting a preapproval inspection of an API.

b. New technology that requires new expertise, significantly new equipment, or new facilities.

c. Changes (particularly those that are not referenced in the DMF or drug application) in starting materials, intermediates, equipment, facilities, support systems, processing steps, packaging materials, or computer software.

7. For foreign firms, obtain file information from the appropriate CDER assessment division or compliance unit. Investigators may also request background information about the site directly from the U.S. Agent before the inspection.

2. Reporting

Investigators should describe their inspection coverage and findings in the EIR. Investigators should include a sufficient level of detail for further FDA evaluation of the firm's state of control and conformance to CGMP requirements. ICH Q7 may be used as a guideline to describe coverage, findings, and deficiencies. However, investigators should not reference specific sections of ICH Q7 in the Form FDA 483 observations or in the EIR. If an investigator believes that a particular practice consistent with ICH Q7 is deficient, the investigator or division should consult with CDER's Office of Manufacturing Quality (OMQ) before making an observation that conflicts with ICH Q7. The Form FDA 483, if issued, should include sections for each of the covered systems. In addition to the IOM format and information reporting requirements, all EIRs for API manufacturers must include:

1. A list of APIs manufactured (or categories of APIs if there are several APIs) along with the general manufacturing process for each API (e.g., chemical synthesis, fermentation, extraction of botanical material).

2. An explanation for the APIs selected for coverage.

3. For foreign API manufacturers, the U.S. Agent's name, title, complete mailing address, telephone number, and fax number or email address.

4. For foreign API manufacturers, a report of all APIs imported into the United States in the last two years, their consignees (including in-country intermediary repackers, relabelers, wholesalers, distributors, and shippers that import directly in the U.S.), and an estimate of the frequency and quantity of shipments to these consignees.

5. A description of each of the systems selected for coverage (i.e., areas, processes, and operations), what was covered, who was interviewed, and what manufacturing activities were taking place during the inspection.

6. Any significant changes to a firm's packaging, labeling, product line, or processes, particularly changes that are not properly filed, submitted, or reported in a DMF or drug application (including changes to APIs intended for use in compounding).

A. Special Instructions for Responding to a Form FDA 483

Investigators should instruct management to submit an electronic response to a Form FDA 483 with appropriate documentation via email to CDER-OC-OMQ-Domestic483Response@fda.hhs.gov or CDER-OC-OMQ-International483Response@fda.hhs.gov.

For human drug inspections that include CGMP and preapproval inspectional coverage, in addition to the address above, include: CDERPAIprogram@fda.hhs.gov.

PART IV – ANALYTICAL

API samples that the investigator collects for quality evaluation should be submitted to the appropriate servicing laboratory. Please email the Office of the Chief Scientist (OCS)/Office of Analytical and Regulatory Laboratories (OARL) at OCOCSOARLProgramCoordinators@fda.hhs.gov to request servicing laboratories for chemical and microbiological testing. In the request, include the API description, lot numbers to be tested, analyses required, and the reason for sample collection. Servicing laboratories will be selected based on specialization, technology and testing expertise, and capacity. However, it should be noted that physical API samples are not required to support regulatory or administrative action against a violative firm or drug.

PART V – REGULATORY/ADMINISTRATIVE STRATEGY

If one or more systems are documented as not in a state of control, OII should endorse an OAI inspection report.

Normally, issuing a warning letter or taking other regulatory or administrative action should result in all profile classes being classified as unacceptable. However, if CDER does not approve a recommendation for a warning letter or other regulatory action, all profile classes should be classified as acceptable.

If an establishment with approved established conditions has an inspection that is classified as OAI and raises significant concerns about the quality system (particularly about the change management system), CDER offices will collaboratively evaluate the significant findings and the firm's response. They will use this information to determine how these findings could potentially affect the approved established conditions.

Records, documents, and other information that are requested and reviewed during remote regulatory assessments may reveal potentially violative practices. In such cases, OMQ's evaluation of a potential OAI recommendation will align with the procedures in this section during review of the case.

Recommendations for regulatory action for API CGMP deficiencies should cite the statute (section 501(a)(2)(B) of the FD&C Act) and not the drug product regulations in parts 210 and 211. These recommendations should not cite ICH Q7; however, they can use ICH Q7 as a guideline for describing the deficiencies. The regulatory action should demonstrate how the observed deficiencies could potentially impact or have already impacted the quality of the API. When evaluating whether to recommend regulatory or administrative action, consider the critical attributes of the API, the significance of its pharmacological activity, and the intended use of the drug product that will contain the API.

Evidence that supports a significant deficiency or pattern of deficiencies within a system may indicate system failure. The failure of a system puts all of the manufacturer's APIs at risk and should be promptly corrected. The following are examples of deficiencies that may result in an inspection that is classified as OAI:

1. Contamination of APIs with filth, objectionable microorganisms, toxic chemicals, or significant amounts of other types of chemicals, or a reasonable potential for such contamination because of a demonstrated route of contamination (facilities and equipment system; production system).

2. Failure to show that API batches conform to established specifications, such as specifications in drug applications, USP specifications, customer specifications, or label claims (quality system).

3. Failure to ensure the accuracy and integrity of data.[39] Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate. Examples of data integrity concerns include failing to scientifically justify not reporting relevant data, altering of raw data, inconsistently documenting manufacturing operations, backdating test results, testing into compliance, and fabricating test results. Examples of failure to ensure the accuracy and integrity of data include systems which allow for the alteration or deletion of raw data, systems without audit trails activated, loose raw data forms without adequate issuance and reconciliation, and inadequate risk-based monitoring for data integrity concerns (all systems).

4. Failure to comply with commitments in drug applications or DMFs. All of the required information in these commitments should be accurate and current. This includes information about the manufacturing process, impurity profiles, and other specifications or procedures associated with the manufacture of the API (quality system).

5. Distribution of an API that does not conform to established specifications (quality system).

6. Deliberate blending of API batches in an attempt to: (1) dilute or hide filth or other noxious contaminants; or (2) disguise a critical quality defect and obtain a batch that meets its specifications (production system).

7. Failure to demonstrate that all materials (including water and any other solvents used in the final step of the API production process) are chemically and microbiologically suitable for their intended use and do not adversely affect the quality of the API (materials system).

8. Lack of adequate validation for critical steps in the API production process, particularly for the final separation and purification of the API or API production processes for which there is evidence that the process is not adequately controlled. Lack of adequate control may be indicated by repeated batch failures or wide variation in final yields compared with the process average over time (quality system; production system).[40]

9. Implementation of retrospective process validation for an existing API production process when the process has changed significantly, the firm lacks impurity profile data, or there is evidence of repeated batch failures because of process variability (quality system; production system).

[39] See the guidance for industry *Data Integrity and Compliance With Drug CGMP: Questions and Answers*.

[40] See the guidance for industry *Process Validation: General Principles and Practices*.

10. Failure to establish an impurity profile for each API production process. FDA expects manufacturers to establish complete impurity profiles for each API as part of the process validation effort. This includes collecting data on: (1) actual and potential organic impurities that may arise during synthesis, purification, and storage of the API; (2) actual and potential inorganic impurities that may arise during the API production process; and (3) organic and inorganic solvents used during the manufacturing process that are known to carry over to the API. Impurity profile testing of each batch or after a specified number of batches may detect new impurities that could be from a deliberate or nondeliberate change in the API manufacturing process (laboratory control system).

11. Failure to show that a reprocessed batch complies with all of the established standards, specifications, and characteristics (quality system; laboratory control system).

12. Failure to test for residues of organic or inorganic solvents used during manufacturing that may carry over to the API using analytical procedures with appropriate levels of sensitivity (laboratory control system).

13. Failure to have a formal process change control system in place to evaluate changes in starting materials, facilities, support systems, equipment, processing steps, and packaging materials that may affect the quality of APIs (all systems).

14. Failure to maintain batch and quality control records (quality system).

15. Incomplete stability studies to establish API stability for the intended period of use, for example, failure to conduct forced degradation studies on APIs to isolate, identify, and quantify potential degradants that may arise during storage (laboratory control system).

16. Use of laboratory test methods that are inadequate or have not been validated, or the use of an inadequately qualified or untraceable reference standard (laboratory control system).

17. Packaging and labeling in a way that introduces a significant risk of mislabeling (packaging and labeling system).

PART VI – REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. References

- Compliance Programs
  - 7346.832—*Preapproval Inspections*
  - 7356.000—*Inspections of CDER-led or CDRH-led Combination Products*
  - 7356.002—*Drug Manufacturing Inspections*
  - 7356.002A—*Sterile Drug Process Inspections*
  - 7356.002M—*Surveillance Inspections of Protein Drug Substance Manufacturers*
- Draft Guidances for Industry[41]
  - *Conducting Remote Regulatory Assessments Questions and Answers* (January 2024)
  - *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021)
- Guidances for Industry
  - *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)
  - *Changes to an Approved NDA or ANDA* (April 2004)
  - *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021)

[41] When final, these guidances will represent FDA's current thinking on this topic.

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

- *Control of Nitrosamine Impurities in Human Drugs* (September 2024)

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

- *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)

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

- *Process Validation: General Principles and Practices* (January 2011)

- *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006)

- *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (August 2023)

- *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (September 2004)

- *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)

- Guidance for Industry and FDA Staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017)

- ICH Guidances for Industry

  - *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023)

- *Q3A Impurities in New Drug Substances*, Revision 2 (June 2008)
- *Q3C(R8) Impurities: Guidance for Residual Solvents* and its *Appendices* (December 2021)
- *Q3D(R2) Elemental Impurities (*September 2022)
- *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,* Revision 1 (September 2016)
- *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Questions and Answers* (April 2018)
- *Q9(R1) Quality Risk Management* (May 2023)
- *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* and its *Annexes* (May 2021)

- *Investigations Operations Manual,* https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual
- *Regulatory Procedures Manual,* https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual
- USP General Chapter <1086> *Impurities in Drug Substances and Drug Products*

2. **Attachments – None.**

3. **Program Contacts**

A. CDER

(1) CGMP or Quality-Related Policy Questions

Please email CDER Office of Pharmaceutical Quality Policy (OPQPolicy@fda.hhs.gov) for questions about the following topics:

- CGMP or quality-related policy
- Technical or scientific information needs (including questions about this compliance program)

(2) Enforcement-Related Guidance or Policy Questions

Office of Compliance

Office of Manufacturing Quality

Please email CDER OMQ Compliance Policy (CDEROMQCompliance@fda.hhs.gov) for questions about the following topics:

- Enforcement-related guidance or policy, including:
  - Evidence needs and sufficiency
  - Citations
  - Case evaluation and/or recommendation advice

(3) Labeling Requirements and Policies

CDER Office of Compliance

Office of Unapproved Drugs and Labeling Compliance

Please email CDEROUDLCPMTRACK@cder.fda.gov for general inquiries.

(4) Registration and Drug Listing Requirements

CDER Office of Compliance

Office of Unapproved Drugs and Labeling Compliance

Please email edrls@fda.hhs.gov for questions and assistance with registration and listings.

B. OII

(1) Inspection-Related Questions

Office of Human and Animal Drug Inspectorate (OHADI)
Division of Human and Animal Drug Global Operations (DHADGO)
Human and Animal Drug Program Operations Branch (HADPOB)
Email: OIIDrugInspectionPOC@fda.hhs.gov

C. Office of the Commissioner

(1) Sampling of APIs

Office of the Chief Scientist (OCS)
Office of Analytical and Regulatory Laboratories (OARL)
Email: OCOCSOARLProgramCoordinators@fda.hhs.gov

PART VII – CENTER RESPONSIBILITIES

Compliance programs 7356.002—*Drug Manufacturing Inspections* and 7346.832—*Preapproval Inspections* describe the responsibilities for each center.