CHAPTER 56—DRUG QUALITY ASSURANCE

SUBJECT:	IMPLEMENTATION DATE:
Drug Manufacturing Inspections REVISION: Revised to add elements of International Council for Harmonisation (ICH) guidances for industry *Q9 Quality Risk Management, Q10 Pharmaceutical Quality System,* and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management;*[1] control of nitrosamine impurities; and alternative tools for evaluating facilities.	10/17/2022

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
All Human Drugs Industry codes: 50, 54-56, 59, 60-66	Domestic/Foreign current good manufacturing practice (CGMP) inspections covered under this compliance program, 7356.002, include inspection of any establishment that does not have a specific program:

PAC	Type	Subject
56002	Full	Drug Process Inspections (DPI)
56002H	Abbreviated	Drug Process Inspections (DPI)

Report CGMP coverage of the programs specified below under PACs as follows (using the appropriate compliance program):

PAC	Type	Subject
56002A	Full	DPI/Small Volume Parenterals (compliance program 7356.002A—*Sterile Drug Process Inspections*)
56002I	Abbreviated	DPI/Small Volume Parenterals (compliance program 7356.002A)
56002B	Full	DPI/Drug Repackers and Relabelers
56002J	Abbreviated	DPI/Drug Repackers and Relabelers
56002C	Full	DPI/Radioactive Drugs
56002K	Abbreviated	DPI/Radioactive Drugs
56002F	Full	Active Pharmaceutical Ingredient Process Inspections
56002L	Abbreviated	Active Pharmaceutical Ingredient Process Inspections

[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.

	56002P	Full	Drug Process Inspections - PET Domestic (compliance program 7356.002P—*PET CGMP Drug Process and Pre-Approval Inspections/Investigations*)
	56002Q	Abbreviated	Drug Process Inspections - PET Domestic (compliance program 7356.002P)
	Note: The following surveillance programs are reported under single PACs; there are no full or abbreviated specific PACs:		
	PAC	**Subject**	
	56002E	DPI/Medical Gas Manufacturers (compliance program 7356.002E—*Compressed Medical Gases*)	
	56002M	DPI/Therapeutic Biological Product Inspections (compliance program 7356.002M—*Surveillance Inspections of Protein Drug Substance Manufacturers*)	
	56002S	Drug Process Inspections - Biosimilars	
	56R927	Remote Interactive Evaluation (RIE) Activities - Human Drugs	
	56R928	704a4 Activities - Human Drugs	

FIELD REPORTING REQUIREMENTS:

The Office of Regulatory Affairs (ORA) division completes the establishment inspection report (EIR), including an inspection classification consistent with Field Management Directive (FMD) 86 and FDA policies governing pharmaceutical quality, including this compliance program, within ORA established timeframes. The ORA division files the inspection documents electronically no later than 45 calendar days from the close of the inspection using the specific module (eNSpect, or Compliance Management System (CMS)) accessible to both ORA and CDER (Center for Drug Evaluation and Research).

ORA divisions should, as soon as practical, report significant inspection issues into eNSpect, as per the *Investigations Operations Manual* (IOM). For inspections initially classified as Official Action Indicated (OAI) due to failure to comply with CGMP requirements, submit the written classification analysis and electronic documents to CDER's Office of Compliance (OC), Office of Manufacturing Quality (OMQ) for evaluation via CMS.[2]

ORA staff (e.g., preapproval program managers (PAMs)) are responsible for timely reporting of potential OAI (pOAI) alerts into Panorama as per current procedures.[3] The ORA PAM should consider the following when entering a pOAI alert into Panorama:

[2] For further information, see Part V—Regulatory/Administrative Strategy.

[3] Panorama is a component of the CDER Informatics Platform that is used to manage workflow and documents. Refer to Panorama step-by-step guides for creating, editing and closing pOAI alerts.

1. For CGMP (surveillance or for-cause) coverage that may result in an OAI status, enter a pOAI alert into Panorama, as soon as practical, but at most within 2 days of closing the inspection.
2. Enter a pOAI alert for the refusal of an inspection.[4]
3. If surveillance and preapproval coverage are provided during the same inspection:
   a. Do not enter a pOAI alert for significant application-specific preapproval issues that do not impact marketed product; refer to compliance program 7346.832—*Preapproval Inspections*.
   b. Do enter a pOAI alert for significant surveillance issues (see point 1).

The ORA PAM must remove the pOAI alert in Panorama as soon as practical if the ORA division decides to change the initial recommendation of OAI. If OMQ decides to change the initial OAI recommendation, OMQ must update or remove the pOAI alert associated with that initial classification in Panorama as soon as practical.

During an inspection, if an inspection team obtains information pertaining to inadequate adverse drug experience reporting, unapproved drug issues, or postapproval reporting violations (e.g., failing to submit application supplements, field alert reports (FARs)), or the team observes significant findings pertinent to the quality information provided in the site dossier, the inspection team should notify the Office of Quality Surveillance (OQS), in CDER's Office of Pharmaceutical Quality (OPQ), and the Office of Compliance in a timely manner by emailing CDERSurveillance@fda.hhs.gov and CDERCompliance@fda.hhs.gov and, for biological products, copying CDERBIOTECHINSPECT@fda.hhs.gov. Notifications should include a summary of the findings and any unreported changes the team believes should have been submitted to FDA per 21 CFR 314.70 or 601.12 (i.e., an annual reportable change, a change being effected supplement, or a prior approval supplement). **The inspection team should not request manufacturing supplements to be submitted unless CDER confirms that such a submission is appropriate.** The inspection team should also document its findings under separate captions in the EIR. Data system information about these inspectional activities should be reported under separate product/assignment codes (PACs). Expansion of coverage under these programs into a CGMP inspection[5] should be reported under this compliance program.

The ORA divisions should use this revised compliance program for all CGMP inspections satisfying the statutory obligation for periodic risk-based inspections of drug production. The instructions provided in this section and elsewhere in this compliance program governing ORA and CDER interactions supersede the instructions in the other compliance programs for the 5600 PACs (e.g., 7356.002A, 7356.002F—*Active Pharmaceutical Ingredient (API) Process Inspection*, 7356.002P).

Note that active pharmaceutical ingredient (API) and positron emission tomography (PET) drug inspections are performed to verify conformance with different quality standards and have their

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

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

own compliance programs. API inspections per compliance program 7356.002F are conducted to verify adherence to section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) using ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* as a guideline. PET inspections per compliance program 7356.002P are conducted to verify adherence to 21 CFR part 212.

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PART I—BACKGROUND

Until 2012, FDA was required to inspect domestic establishments[6] that manufacture drugs marketed in the United States every 2 years, but there was no comparable requirement for inspecting foreign establishments. The Food and Drug Administration Safety and Innovation Act (FDASIA),[7] which amended section 510(h) of the FD&C Act, eliminated this distinction, directing FDA to take a risk-based approach to inspecting both domestic and foreign drug manufacturing establishments. The selection of both domestic and foreign establishments for routine surveillance inspections is now driven by a risk-based site selection model. In 2015, FDA formalized its process for selecting establishments for inspection based on risk factors specified by section 510(h) of the FD&C Act.

FDASIA also amended the FD&C Act to provide FDA the authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities if FDA determines those authorities are capable of conducting inspections that meet U.S. requirements. Under section 809(a)(1) of the FD&C Act, FDA may enter into arrangements and agreements with a foreign government or an agency of a foreign government to recognize the inspection of a foreign establishment registered under section 510(i) of the FD&C Act to facilitate risk-based inspections in accordance with the schedule established in paragraph (2) or (3) of section 510(h) of the FD&C Act.

This compliance program provides CGMP inspection coverage of drug manufacturing establishments to determine whether they are complying with CGMP requirements per section 501(a)(2)(B) of the FD&C Act, implementing regulations and corrective actions. The focus of CGMP inspections is on system-wide controls that ensure manufacturing processes consistently produce quality drugs. Systems examined during these inspections include those related to quality, facilities and equipment, materials, production, packaging and labeling, and laboratory controls.

FDA expects that establishments that comply with CGMP requirements are those that operate in a state of control and consistently manufacture drug products of acceptable quality. FDA will use information gathered from inspections under this compliance program to assess an establishment's compliance with CGMP requirements, including, among other things, evaluating the effectiveness of the establishment's quality system.[8] FDA will also use this information to assess whether the quality system exceeds CGMP requirements. In total, this information will support the implementation of ICH Q12 and help FDA assess manufacturing establishments in support of regulatory decisions.

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[6] In this compliance program, the synonymous terms *establishment*, *person*, *site*, *firm*, and *facility* cover entities subject to FDA drug manufacturing regulations and statutory authority.

[7] See https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf, page 1067.

[8] In this compliance program, the term *quality system* refers to the pharmaceutical quality system (PQS) as described in ICH Q10 and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) recommendation PI 054-1 *How To Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management*, https://picscheme.org/docview/4294. The PQS is a management system to direct and control a pharmaceutical company with regard to quality.

Inspections under this compliance program serve a core role in determining an establishment's compliance with CGMP requirements. As part of a holistic approach, FDA may use other information sources to assist in our evaluation of the CGMP compliance of an establishment, including (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 (MRAs) and other confidentiality agreements;[9] and (3) remote regulatory assessments (RRAs),[10] including (a) records or other information requested directly from facilities and other inspected entities under section 704(a)(4) of the FD&C Act, and (b) remote interactive evaluations (RIEs) conducted where appropriate.

The inspectional guidance and instructions in this compliance program are structured to provide for efficient use of resources devoted to routine surveillance coverage, recognizing that in-depth coverage of all systems and all processes is not feasible or required for all establishments and inspections. This compliance program also provides instruction for conducting for-cause inspections as appropriate (see Part II.3—Program Management Instructions).

[9] 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.

[10] 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. Objectives

The goal of this compliance program's activities is to ensure that establishments consistently manufacture drug products of acceptable quality and minimize consumers' exposure to adulterated drug products.

Under this compliance program, inspections, investigations, sample collections, sample analyses, and regulatory or administrative follow-up are made to identify quality problems and adverse trends at establishments, so that FDA can develop strategies to mitigate them. In addition to inspections conducted by FDA staff and inspections conducted by foreign regulatory authorities under MRAs, when appropriate, FDA may also use RRAs as part of the regulatory oversight program to support regulatory decisions, inform inspection planning, and verify certain information submitted to the Agency (see Attachment A for RRAs).

The objectives of this compliance program follow:

- Determine whether inspected establishments are operating in compliance with applicable CGMP requirements and, if not, provide the evidence for actions to prevent adulterated products from entering the market. As appropriate, remove adulterated products from the market, and take action against persons responsible.
- Provide an assessment of establishments' conformance to CGMP requirements for Agency decisions.
- Gain insight into the effectiveness of a drug manufacturer's quality system. In addition, it may inform understanding, to the extent possible, of practices at a facility that not only support meeting CGMP compliance requirements to establish and maintain a robust state of control but also promote a quality culture that allows for exceeding this standard.
- Provide input to establishments during inspections to improve their compliance with regulations.
- Better understand current practices in drug manufacturing for the purpose of updating CGMP requirements, regulatory policy, and guidance documents.

2. Strategy

A. Inspection of Manufacturing Establishments

Drug products are manufactured using many physical operations that bring together components, containers, and closures to make a product that is released for distribution. Drug manufacturing can be organized into sets of operations and related activities, called systems. Control of all systems helps to ensure the establishment will produce drugs that are safe and that meet the identity, strength, quality, and purity characteristics as intended.

This compliance program applies to all pharmaceutical manufacturing operations at the establishment, which includes repackaging, contract testing, labeling, and other operations.

It is not practical for FDA to audit every aspect of CGMP in every manufacturing establishment during every inspection visit. Profile classes generalize inspection coverage from a small number of specific products to all the products in that class. Reporting coverage for every profile class as defined in eNSpect, for each inspection, provides the most broadly resource-efficient approach. This compliance program uses a risk-based systems approach to further generalize inspection coverage from a small number of profile classes to an overall evaluation of the establishment. Risk-based inspectional approaches allow updating of all profile classes.

The inspection is defined as audit coverage of two or more systems, with mandatory coverage of the quality system (see system definitions below). Depending on the purpose of the inspection, inspection coverage may include different numbers of systems. Inspecting the minimum number of systems, or more systems as deemed necessary by the ORA division, will provide the basis for an overall CGMP classification decision.

B. Inspection of Systems

Inspections of drug manufacturers should be made and reported using the system definitions and industry codes in this compliance program. Focusing on systems, rather than profile classes, will increase efficiency in conducting inspections because the systems are often applicable to multiple profile classes. System inspection coverage should represent all profile classes at the establishment and determine their acceptability/non-acceptability.

Coverage of a system should be sufficiently detailed, with specific examples selected, so that the system inspection outcome reflects the state of control in that system for every profile class. If a particular system is adequate, it should be adequate for all profile classes manufactured by the establishment. For example, the way an establishment handles “materials” (i.e., receipt, sampling, testing, acceptance, etc.) should be the same for all profile classes. An inspection does not have to include every profile class attribute when covering a given system provided that inspection coverage includes related controls for all types of drugs and operations. Likewise in the production system, there are general requirements like use of standard operating procedures (SOPs), charge-in of components, equipment identification, in-process sampling, and testing that can be evaluated through selection of example products in various profile classes. Under each system, there may be something unique for a particular profile class: e.g., under the materials system, the production of Water for Injection USP (United States Pharmacopeia) for use in manufacturing. Selecting unique functions within a system will be at the discretion of the lead investigator. Any given inspection need not cover every system. See Part III of this compliance program.

Complete inspection of one system may necessitate further follow up of some items within the activities of other systems to fully document the findings. However, this coverage does not constitute nor require complete coverage of these other systems.

C. Scheme of Systems for the Manufacture of Drugs/Drug Products

The overall theme in devising the following scheme of systems was the subchapter structure of the 21 CFR part 211 CGMP regulations. Every effort was made to group whole subchapters

together in a rational set of six systems numbered below that incorporates the general scheme of pharmaceutical manufacturing operations.

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, and distribution records required to be maintained by the CGMP regulations and selected for review should be included for inspection audit within the context of each of the six systems. Inspections of contract companies should be within the system for which the product or service is contracted as well as their quality system.

A general scheme of systems for auditing the manufacture of drugs and drug products consists of the following:

1. **Quality System.** This system ensures overall compliance with CGMP 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.[11] This system also includes the quality unit and its review and approval duties (e.g., quality agreements, change management, risk management, reprocessing, batch release, annual record review, investigations, continued process verification, validation protocols and reports). It includes product defect evaluations and evaluations of returned and salvaged drug products. See the CGMP regulations, 21 CFR part 211, subparts B, E, F, G, I, J, and K.
2. **Facilities and Equipment System.** This system includes the measures and activities that provide an appropriate physical environment and resources used in the production of drugs or drug products. It includes the following:
    a. Buildings and facilities along with maintenance
    b. Equipment qualifications (installation and operation), equipment calibration and preventive maintenance, and cleaning and validation of cleaning processes as appropriate; process performance qualification will be evaluated as part of the inspection of the overall process validation, which is done within the system where the process is employed
    c. Utilities that are not intended to be incorporated into the product, such as HVAC, compressed gases, steam, and water systems

    See the CGMP regulations, 21 CFR part 211, subparts B, C, D, and J.
3. **Materials System.** This system includes measures and activities to control finished products, components (including water or gases that are incorporated into the product), containers, and closures. It includes validation of computerized inventory control processes; management of lifecycle risks from components, containers, and closures;

[11] *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.

drug storage; distribution controls; and records. See the CGMP regulations, 21 CFR part 211, subparts B, E, H, and J.

4. **Production System.** This system includes measures and activities to control the manufacture of drugs and drug products, including batch compounding, dosage form production, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved manufacturing procedures. See the CGMP regulations, 21 CFR part 211, subparts B, F, and J.
5. **Packaging and Labeling System.** This system includes measures and activities that control the packaging and labeling of drugs and drug products. It includes written procedures, label examination and usage, label storage and issuance, packaging and labeling operations controls, and validation of these operations. See the CGMP regulations, 21 CFR part 211, subparts B, G, and J.
6. **Laboratory Control System.** This system includes measures and activities related to laboratory procedures, testing, analytical methods development and validation or verification, and the stability program. See the CGMP regulations, 21 CFR part 211, subparts B, I, J, and K.

3. Program Management Instructions

A. Definitions

(1) Surveillance Inspections

(a) Full Inspection Option

The full surveillance inspection option is a CGMP inspection meant to provide 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 of the ORA division. During the course of a full inspection, verification of quality system activities may require limited coverage in other systems. The full inspection option will normally include an inspection audit of at least four of the systems, one of which must be the quality system (the system that includes management's responsibility for overseeing an ongoing state of control).

(b) Abbreviated Inspection Option

The abbreviated surveillance inspection option is a CGMP inspection meant to provide an efficient, updated evaluation of an establishment's conformance with CGMP requirements. The abbreviated inspection will provide documentation for continuing an establishment in a satisfactory CGMP compliance status. Generally, this will be done when an establishment has a record of satisfactory CGMP compliance, with no significant recall, or product defect or alert incidents, or with little shift in the manufacturing profiles of the establishment since the last inspection. See Part III.2.B—Selecting the Abbreviated Inspection Option. An abbreviated inspection may change to a full inspection, upon findings of objectionable conditions (as listed in Part V) in one or more systems, with ORA division concurrence. The abbreviated inspection

option normally will include an inspection audit of at least two of the systems, one of which must be the quality system (the system that includes management's responsibility for overseeing an ongoing state of control). The ORA division drug program managers 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. Some establishments participate in a limited part of the production of a drug or drug product, e.g., a contract laboratory. Such establishments may employ only two of the systems defined. In these cases, the inspection of the two systems will comprise inspection of the entire establishment and will be considered the full inspection option.

(c) Selecting Systems for Coverage

The ORA division will select systems for coverage based on the establishment's specific operation, history of previous coverage, history of compliance, or other priorities determined by the ORA division.

(2) For-Cause Inspections

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

For-cause inspections that are to be initiated and reported under this compliance program fall under the category of follow-up CGMP compliance inspections performed to verify corrective actions after a regulatory action has been taken. Follow-up CGMP compliance inspections provide focused coverage and include the areas of concern, the proposed corrective action plan for impacted operations, any implemented corrective actions, and/or the deficiencies noted on Form FDA 483 for a previous inspection. The decision to add systems coverage is made on a case-by-case basis.

For-cause inspections in response to FARs are to be initiated and performed under compliance program 7356.021—*Drug Quality Reporting System (DQRS) (MedWatch Reports); NDA Field Alert Reports (FARs)*.[12]

Other for-cause inspections (e.g., industry complaints, other indicators of defective products) may be initiated as per FMD 17 but expanded to include CGMP coverage for the purpose of updating overall compliance status.

(3) State of Control

A drug establishment is considered to be operating in a state of control when it employs conditions and practices that comply with section 501(a)(2)(B) of the FD&C Act and the portions of the CGMP regulations that pertain to its systems. An establishment in a state of

[12] NDA=new drug application.

control produces finished drug products for which there is an adequate level of assurance of quality, strength, identity, and purity.

An establishment is out of control if any one system is out of control. A system is out of control if the quality, identity, strength, and purity of the products resulting from one or more systems 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 demonstrating an out-of-control system or systems.

(4) Drug Process

A drug process is a related series of operations that result in the preparation of a drug or drug product. Major operations or steps in a drug process may include mixing, granulation, encapsulation, tableting, chemical synthesis, fermentation, aseptic filling, sterilization, packaging, labeling, testing, and so forth.

(5) Drug Manufacturing Inspection

A drug manufacturing inspection is an establishment inspection in which two or more systems, including the quality system, are evaluated to determine if manufacturing is occurring in a state of control.

B. Inspection Planning

ORA will conduct drug manufacturing inspections using a risk-based approach and will maintain profiles or other monitoring systems. The ORA division is responsible for determining the depth of coverage given to each drug establishment. The depth of inspection coverage should be determined by the establishment's compliance history, the manufacturing technology employed, and the characteristics of the products. CGMP inspectional coverage must be sufficient to assess the state of control and compliance for each establishment.

Before scheduling the surveillance coverage of the newly registered establishment, the investigator should consult with their ORA division to determine whether there have been any requests for preapproval or postapproval inspections that should be included in the inspectional coverage. In advance of a scheduled surveillance inspection, OQS prepares an up-to-date site dossier that includes, but is not limited to, quality information on establishment inspection history, recalls, shortages, customer complaints, foreign regulator inspection outcomes, information on submitted FARs or BPDRs, a listing of all products manufactured at the site, and, where applicable, CGMP elements identified as at risk. When a system is inspected, the inspection of that system may be considered applicable to all products that use it. Investigators should select an adequate number and type of products to accomplish coverage of the system. Selection of products should be made so that coverage is representative of the establishment's overall abilities in manufacturing within CGMP requirements.

Products posing special challenges, such as low dose products, narrow therapeutic range drugs, combination products,[13] modified release products, biological products, and new products manufactured under recently approved drug applications, should be considered first in selecting products for coverage. Refer to IOM chapter 5, section 5.5.1.2—Inspectional Approach.[14]

The health significance of certain CGMP deviations may be lower when the drug product involved has no major systemic health effect or no dosage limitations such as in products like calamine lotion. Such products should be given inspection coverage with appropriate priority.

Inspections for this compliance program may be performed during visits to an establishment when operations are being performed for other compliance programs or other investigations.

C. Profiles

The inspection findings will be used as the basis for updating all profile classes in the profile tab in eNSpect as per the IOM. Normally, an inspection under this risk-based systems approach will result in all profile classes being updated.

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

[14] See https://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM150576.pdf.

PART III—INSPECTIONAL

1. General

The investigator should review and use the CGMP regulations for finished pharmaceuticals (21 CFR parts 210 and 211) and related guidance for industry to evaluate manufacturing processes.

The investigator should conduct inspections according to Part II.2—Strategy of this compliance program. Recognizing that drug establishments vary greatly in size and scope, and manufacturing systems are more or less sophisticated, the approach to inspecting each establishment should be carefully planned. The complexity and variability necessitate a flexible inspection approach—one that allows the investigator to choose the inspection focus and depth appropriate for a specific establishment, but also one that directs the performance and reporting on the inspection within a framework that will provide for a uniform level of CGMP assessment, efficient communication, and evaluation of findings. Performance and documentation under this compliance program may be facilitated by the use of applicable eNSpect inspection protocols along with the collection of evidence.

Inspectional observations noting CGMP deficiencies should be related to a requirement. CGMP requirements for manufacture of drug products (dosage forms) are in section 501(a)(2)(B) of the FD&C Act and the regulations and are amplified by guidance, case precedents, and so forth. CGMP requirements apply to the manufacture of all human drugs, which include prescription and nonprescription drug products, drug products that are the subject of pending applications, drug products used in clinical trials, and products not requiring approval.

API and PET drug inspections are performed to verify conformance with different quality standards than 21 CFR parts 210 and 211 and have their own compliance programs. API inspections are conducted under compliance program 7356.002F, which employs ICH Q7 as a quality standard and establishes compliance to the statutory requirement of section 501(a)(2)(B) of the FD&C Act. Establishments that follow ICH Q7 generally will be considered to comply with the statutory requirement. PET inspections under compliance program 7356.002P are conducted to verify adherence to 21 CFR part 212.

Guidance documents are not to be referred to as the justification for an inspectional observation. The justification comes from the statute and the CGMP regulations. Current guides to inspection and guidance documents provide interpretations of requirements, which may assist in the evaluation of the adequacy of CGMP systems. Guidance documents do not establish requirements.

Current inspectional observation policy as stated in the IOM says that Form FDA 483, when issued, should be specific and contain only significant items. For this compliance program, inspection observations should be organized under separate captions by the systems defined in this compliance program. List the observations in order of importance within each system. Where repeated or similar observations are made, they should be consolidated under a unified observation. A limited number of observations can be common to more than one system (e.g., organization and personnel, including appropriate qualifications and training). In these instances, put the observation in the first system reported on Form FDA 483 and in the text of the EIR, and

reference the applicability to other systems where appropriate. This is being done to accommodate the structure of eNSpect, which allows individual citation once per Form FDA 483. Refrain from using unsubstantiated conclusions. Do not use the term *inadequate* without explaining why and how. Refer to policy in IOM chapter 5, section 5.2.3—Reports of Observations, for further guidance on the content of inspectional observations.

Specific, specialized inspectional guidance may be provided in addition to this compliance program or in requests for inspection, assignments, and so forth.

2. Inspection Approaches

This compliance program provides two CGMP inspection options: Full and abbreviated. See the definitions of the inspection options in Part II of this compliance program.

A. Selecting the Full Inspection Option

The full inspection option will include inspection of at least four of the systems listed in Part II.2—Strategy, one of which must be the quality system.

- Select the full inspection option for an initial FDA inspection of newly registered establishments. Inspection coverage should include all systems as appropriate to the operations. A full inspection may change to an abbreviated inspection, with **ORA division concurrence** and where appropriate.
- Select the full inspection option when the establishment has a history of fluctuating into and out of compliance. To determine if the establishment meets this criterion, the ORA division should use all information at its disposal, such as inspection results, results of sample analyses, complaints, defects, DQRS reports and BPDRs, recalls, and any compliance actions resulting from them or from past inspections.
- Evaluate whether important changes have occurred by comparing current operations against the EIR for the previous full inspection. The following types of changes are typical of those that warrant the full inspection option:
  - New potential for cross-contamination arising through change in process or product line
  - Use of new technology requiring new expertise, significant new equipment, or new facilities
- A full inspection may also be conducted on a surveillance basis at the ORA division's discretion.

B. Selecting the Abbreviated Inspection Option

The abbreviated inspection option normally will include an inspection audit of at least two systems, one of which must be the quality system. During the course of an abbreviated

inspection, verification of quality system activities may require limited coverage in other systems.

- This option involves inspecting the manufacturer to maintain surveillance over the establishment's manufacturing practices and quality performance and to evaluate whether the establishment is maintaining and improving the CGMP level of assurance of product quality.
- Select the abbreviated inspection option with ORA division concurrence when an establishment has a record of sustained acceptable compliance history, a strong risk management program, and a lack of significant marketed product quality defects.
- Abbreviated inspection coverage may be changed to full inspection coverage at the discretion of the ORA division.

C. Inspection Coverage

It is not anticipated that full inspections (4 to 6 systems coverage) can be conducted every time. To build comprehensive information on the establishment's manufacturing activities, ORA divisions should consider selecting different systems for inspection coverage during successive abbreviated inspections.

Follow-up inspections to a warning letter or other significant regulatory actions are 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 the discretion of the ORA division before or during the inspection.

3. System Inspection Coverage

A. Quality System

For the purposes of this compliance program, *quality system* refers to the system (i.e., policies, procedures, controls, activities, etc.) satisfying the specific quality control and quality assurance requirements outlined under 21 CFR 211.22, as well as other quality-related requirements in 21 CFR part 211 and under the FD&C Act.

The quality system, typically described in an establishment's quality manual, should provide for effective senior management oversight of drug quality and support the establishment's quality unit. This includes, but is not limited to, quality policies, quality planning, quality resource management, and quality management review. When effectively implemented with an established quality policy endorsed by senior management, a quality system provides for coordination and direction of the organization's activities related to producing quality drugs, helps establish and maintain a state of control, promotes robust risk management, and facilitates continual improvement throughout a product's lifecycle. To ensure the implementation of a CGMP-compliant quality system, manufacturers should use knowledge management and quality risk management tools to conduct operations, in whole or in part, consistent with

recommendations in guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* and ICH Q9, Q10, and Q12.

Additionally, an inspection conducted under this compliance program provides an opportunity for investigators to observe and document examples of mature quality practices that exceed CGMP requirements and are indicative of an advanced quality system. To aid investigators, Attachment B provides some examples of these practices that, when properly implemented, are indicators of an advanced quality system. The information from this compliance program, when combined with information on mature quality practices gathered from other sources, provides FDA with a more comprehensive understanding of a firm's quality system. This knowledge is used by the Agency to support regulatory decisions, including the use of more flexible approaches in our regulatory oversight.[15]

As described in 21 CFR 314.70(a) (for NDAs) and 314.97(a) (for ANDAs), applicants of approved products "must notify FDA about each change in each condition established in an approved [A]NDA beyond the variations already provided for in the [A]NDA." Similar requirements exist for biologics license application products in 21 CFR 601.12. ICH Q12 and the draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (ICH Q12 implementation guidance)[16] provide an opportunity for applicants to specifically define established conditions (ECs) to 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, but where proposed, they must be approved with the application to be implemented. Some applicants also have approved reporting categories for changes to ECs following the principles outlined in ICH Q12. Applicants include the list of ECs, their reporting categories, and any comparability protocols in the product lifecycle management (PLCM) document.[17] The implementation of a robust change management system that evaluates manufacturing changes in a manner commensurate with the level of risk imposed by a proposed change is a basic element of the quality system and is necessary to support ICH Q12 tools, including ECs, reporting categories for changes to ECs, and comparability protocols.

Inspectional assessment of the quality system is two-phased. The first phase is to evaluate whether the quality unit has fulfilled the responsibility to review and approve all procedures related to manufacturing, quality control, and quality assurance and ensure the procedures are adequate for their intended use as outlined under 21 CFR 211.22(a) and 211.22(c). This also includes the associated recordkeeping systems. The second phase is to assess the data collected to identify quality problems that may link to other major systems for inspectional coverage.

For each of the following, the establishment should have written and approved procedures and documentation resulting therefrom. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished

[15] See ICH Q10, ICH Q12, and OPQ's white paper *Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals*.

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

[17] Comparability protocols may also be described as postapproval change management protocols (PACMP) as described in ICH Q12. These are equivalent terms.

products but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other major systems that would warrant expansion of coverage. All areas under this system should be covered; however, the depth of coverage may vary depending on inspectional findings.

- Quality oversight of contracted operations and material suppliers: Effective monitoring strategy has been implemented; incoming material monitoring, lifecycle qualification program, quality agreements, and timely communication mechanisms are included
- Management oversight of the development, implementation, monitoring, and continual improvement of the quality system: Quality risk management and knowledge management[18] are incorporated (e.g., providing an early warning system for appropriate resource allocation)
- Quality risk management program:
    - Documented and implemented to ensure hazards (e.g., cross-contamination, adulteration, hazardous impurities such as nitrosamines,[19] nitrosating agents, nitrites, nitrates, and azides) are identified, evaluated, addressed, communicated (to the establishment's management and FDA), and continuously reviewed as needed throughout a product's lifecycle
    - Hazardous impurity risk is assessed and control strategies are implemented to mitigate the risk (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 a product's lifecycle
- Product reviews: Conducted at least annually; product quality is reviewed to assess risk and determine the need for changes, such as changes in drug product specifications, manufacturing, or control procedures; statistical analysis is conducted to identify areas (e.g., trends, patterns, correlations, anomalies) for action and improvement; refer to 21 CFR 211.180(e)
- Complaint reviews (quality and medical): Documented; evaluated; investigated in a timely manner; corrective action is included where appropriate
- Discrepancy and failure investigations: Documented; investigated in a timely manner using scientific evidence to identify the root cause; corrective actions and preventive actions (CAPAs) are included and effectiveness of the CAPAs is evaluated
- Change management for the manufacturing of all products: Documented (with justification); quality risk management[20] is used to evaluate proposed changes for

[18] 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.

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

[20] See PIC/S recommendation PI 054-1 *How To Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management.*

potential risks (e.g., hazardous impurities) and impact on product quality; reviewed by subject matter experts; approved before implementation; evaluated for effectiveness; revalidated, reverified, requalified as needed; changes are reported to FDA as appropriate

- Reporting of changes for approved application products: Changes to ECs are documented and reported as defined by the PLCM document in the application or as described in the regulations and existing guidance[21]
- Rejects: Investigation is expanded where warranted; CAPAs are implemented where appropriate
- Stability failures: Investigation is expanded where warranted; need for FARs, BPDRs, and recalls are evaluated; disposition is documented
- Quarantine products
- Validation: Approval of required validation/revalidation (e.g., computer, manufacturing process, laboratory methods) is documented
- Training/qualification of employees in CGMP: Includes coverage of quality functions, risk management, and specific CGMP operations assigned to individual employees
- Programs for the ongoing monitoring of process performance and product quality throughout a product's lifecycle: Significant issues are escalated to senior management
- Reprocess/Rework: Evaluation is conducted and approval is documented; impact on validation and stability is assessed
- Returns/Salvages: Assessment is conducted; investigation is expanded where warranted; disposition is completed

B. Facilities and Equipment System

For each of the following, the establishment should have written and approved procedures and documentation resulting therefrom. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the quality system, all areas listed below should be covered; however, the depth of coverage may vary depending on inspectional findings.

[21] 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, Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products,* and *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports*.

(1) Facilities

- Cleaning and maintenance
- Facility layout and air handling systems for prevention of cross-contamination (e.g., penicillin, beta-lactams, steroids, hormones, cytotoxics)
- Specifically designed areas for the manufacturing operations performed by the establishment to prevent cross-contamination or mix-ups
- General air handling systems
- Control system for implementing changes in the building
- Lighting, potable water, washing and toilet facilities, sewage and refuse disposal
- Sanitation of the building, use of rodenticides, fungicides, insecticides, cleaning and sanitizing agents
- Oversight of facility infrastructure and suitability of manufacturing operations by responsible operations managers

(2) Equipment

- Equipment installation and operational qualification where appropriate
- Adequacy of equipment design, size, and location
- Equipment surfaces that are not reactive, additive, or absorptive
- Appropriate use of equipment operations substances (e.g., lubricants, coolants, refrigerants) contacting products/containers
- Cleaning procedures and cleaning validation for reusable or multiproduct equipment
- Controls to prevent contamination, particularly with pesticides or other toxic materials, or other drug or non-drug chemicals
- Qualification, calibration, and maintenance of storage equipment (e.g., refrigerators, freezers) for ensuring that standards, raw materials, reagents, and so forth are stored at the proper temperatures
- Equipment qualification, calibration, and maintenance, including computer qualification/validation and security
- Control system for implementing changes in the equipment
- Equipment identification practices (where appropriate)
- Documented investigation into unexpected discrepancies

C. Materials System

For each of the following, the establishment should have written and approved procedures and documentation resulting therefrom. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the quality system, all areas listed below should be covered; however, the depth of coverage may vary depending on inspectional findings.

- Training/qualification of personnel
- Identification of components, containers, and closures
- Inventory of components, containers, and closures
- Storage conditions
- Storage under quarantine until tested or examined and released
- Representative samples collected, tested, or examined using appropriate means
- At least one specific identity test conducted on each lot of each component
- Visual identification conducted on each lot of containers and closures
- Testing or validation of supplier's test results for components, containers, and closures
- Rejection of components, containers, and closures not meeting acceptance requirements
- Full investigation of the establishment's procedures for verification of the source of components
- Appropriate retesting/reexamination of components, containers, and closures
- First in—first out use of components, containers, and closures
- Quarantine of rejected materials
- Water and process gas supply, design, maintenance, validation, and operation
- Containers and closures are not additive, reactive, or absorptive to the drug product
- Control system for implementing changes in the materials handling operations
- Qualification/validation and security of computerized or automated processes
- Finished product distribution records by lot
- Documented investigation into unexpected discrepancies
- Risk management program for components: Documented when unacceptable levels of hazardous impurities are identified by the establishment and updated as needed throughout the product's lifecycle

D. Production System

For each of the following, the establishment should have written and approved procedures and documentation resulting therefrom. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the quality system, all areas listed below should be covered; however, the depth of coverage may vary depending on inspectional findings.

- Training/qualification of personnel
- Control system for implementing changes in processes
- Adequate procedure and practice for charge-in of components
- Formulation/manufacturing at not less than 100 percent
- Identification of equipment with contents and, where appropriate, phase of manufacturing or status
- Validation and verification of cleaning/sterilization/depyrogenation of containers and closures
- Calculation and documentation of actual yields and percentage of theoretical yields
- Contemporaneous and complete batch production documentation
- Established time limits for completion of phases of production
- Implementation and documentation of in-process controls, tests, and examinations (e.g., pH, adequacy of mix, weight variation, clarity)
- Justification and consistency of in-process specifications and drug product final specifications
- Prevention of objectionable microorganisms in non-sterile drug products
- Adherence to preprocessing procedures (e.g., set-up, line clearance)
- Equipment cleaning and use logs
- Master production and control records
- Batch production and control records
- Process validation, including validation and security of computerized or automated processes
- Ongoing statistical evaluations (e.g., batch control data, periodic capability analysis) to identify processes that exhibit higher variability and trigger needed improvements
- Change control; the need for revalidation evaluated

- Investigation into unexpected discrepancies
- Effective control strategy established for operations at risk of forming hazardous impurities

E. Packaging and Labeling System

For each of the following, the establishment should have written and approved procedures and documentation resulting therefrom. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the quality system, all areas listed below should be covered; however, the depth of coverage may vary depending on inspectional findings.

- Training/qualification of personnel
- Acceptance operations for packaging and labeling materials
- Control system for implementing changes in packaging and labeling operations
- Adequate storage for labels and labeling, both approved and returned after issued
- Control of labels that are similar in size, shape, and color for different products
- Finished product cut labels for immediate containers that are similar in appearance without some type of 100 percent electronic or visual verification system or the use of dedicated lines
- Gang printing of labels is not done, unless they are differentiated by size, shape, or color
- Control of filled unlabeled containers that are later labeled under multiple private labels
- Adequate packaging records that will 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 product
- Adequate inspection (proofing) of incoming labeling
- Use of lot numbers, destruction of excess labeling bearing lot/control numbers
- Physical/spatial separation between different labeling and packaging lines
- Monitoring of printing devices associated with manufacturing lines
- Line clearance, inspection, and documentation
- Adequate expiration dates on the label

- Conformance to tamper-resistant packaging requirements (see 21 CFR 211.132 and CPG Sec. 450.500 *Tamper-Resistant Packaging Requirements for Certain Over-the-Counter Human Drug Products*)[22]
- Validation of packaging and labeling operations, including validation and security of computerized processes
- Documented investigation into unexpected discrepancies

F. Laboratory Control System

For each of the following, the establishment should have written and approved procedures and documentation resulting therefrom. The establishment's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the quality system, all areas listed below should be covered; however, the depth of coverage may vary depending on inspectional findings.

- Training/qualification of personnel
- Adequacy of staffing for laboratory operations
- Adequacy of equipment and facility for intended use
- Calibration and maintenance programs for analytical instruments and equipment
- Validation and security of computerized or automated processes
- Reference standards; source, purity, and assay and tests to establish equivalency to current official reference standards as appropriate
- System suitability checks on chromatographic systems (e.g., gas chromatography, high-performance liquid chromatography)
- Specifications, standards, and representative sampling plans
- Control strategy established for hazardous impurities if identified in components or the finished product, or as a degradant, throughout the product's lifecycle
- Adherence to the written methods of analysis
- Validation/verification of analytical methods
- Control system for implementing changes in laboratory operations
- Required testing performed on the correct samples
- Documented investigation into unexpected discrepancies

[22] See https://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074391.htm.

- Complete analytical records from tests and summaries of results
- Quality and retention of raw data (e.g., chromatograms and spectra)
- Correlation of result summaries to raw data; presence of unused data
- Adherence to an adequate out-of-specification (OOS) procedure that includes timely completion of the investigation
- Adequate reserve samples; documentation of reserve sample examination
- Stability testing program, including demonstration of stability indicating capability of the test methods

4. Sampling

Samples of defective product 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 the program coordinator (chemistry, microbiology) in the Office of Medical Products, Tobacco, and Specialty Laboratory Operations (OMPTSLO) in ORA's Office of Regulatory Science (ORS) identified in Part VI.3—Contacts for guidance and types of samples (in-process or finished product) to be collected and for the appropriate 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.

When a large number of products have been produced under deficient controls, collect physical or documentary samples of products that have the greatest therapeutic significance, narrow therapeutic range, or low dosage strength. Include samples of products of minimal therapeutic significance only when they illustrate highly significant CGMP deficiencies.

For sampling guidance, refer to IOM chapter 4—Sampling.

5. Inspection Teams

An inspection team (see IOM chapter 5, section 5.1.2.5—Team Inspections) is composed of experts from across ORA, and in certain cases CDER, when specific expertise and experience are needed. Contact ORA's Office of Pharmaceutical Quality Operations if technical assistance is needed (see also FMD 142). ORA leads the inspection with CDER participation, when requested by ORA. Participation of an analyst (chemist or microbiologist) on an inspection team is also encouraged, especially where laboratory issues are extensive or complex. Contact your drug servicing laboratory or ORA/ORS. Each inspection team member is responsible for preparing for, executing, and documenting the inspection, including contributing to the EIR, which documents the items covered during the inspection, within established timeframes.

6. Reporting

If ORA observes critical conditions (e.g., conditions that may result in an imminent health hazard), as appropriate and if feasible, they may be discussed between ORA and OMQ before the inspection closes. The ORA Director of the Investigations Branch or designee, the investigator(s), and OMQ collaboratively decide whether to continue the inspection to gather additional information or to close the inspection to initiate prompt regulatory action.

The investigator will use IOM subchapter 5.11—Reporting for guidance in reporting of inspectional findings. Identify systems covered in the summary of findings. Identify and explain in the body of the report the rationale for inspecting the profile classes covered. Report and discuss in full any adverse findings by systems under separate captions. Add additional information as needed or desired, for example, a description of any significant changes that have occurred since previous inspections. Each report should include a description of operations, products, and controls covered during the inspection in sufficient detail to enable appropriate regulatory decision-making following the inspection and to inform future inspections.

FDA's pharmaceutical CGMP inspection program and resulting inspection reports are of interest to counterpart inspectorates and regulators worldwide who use and rely on FDA inspections and inspection reports, as does FDA of their inspections and reports.

Reports with specific, specialized information required should be prepared as instructed within the individual assignment/attachment.

PART IV—ANALYTICAL

1. Analyzing Laboratories

The types of analyses that may be performed under this compliance program include (but are not limited to):

- Routine analyses: Assay, impurities, dissolution, identification
- Routine microbiological analyses: Sterility, endotoxin, nonsterile examination
- Other microbiological examinations
- Chemical cross contamination
- Antibiotics
- Bioassays
- Particulate matter in injectables

Email ORS/OMPTSLO at ORSOMPSLOProgramCoordinators@fda.hhs.gov for servicing laboratories for chemical and microbiological testing. When contacting ORS for servicing laboratories, provide a product description, lots to be tested, analyses to be performed, and a reason for the sample collection. Servicing laboratories will be identified based on lab specialization, technology and testing expertise, and laboratory capacity.

Note: The Laboratory Servicing Table (LST) Dashboard is not sufficiently detailed to accurately identify laboratories and should not be used for selecting servicing laboratories under this compliance program.

2. Analysis

1. Samples are to be examined for compliance with applicable specifications as they relate to deficiencies noted during the inspection. All analyses will be performed by the official regulatory methods or, when no official method exists, by other validated procedures identified by ORS/OMPTSLO.
2. The presence of cross-contamination should be confirmed bya mass spectroscopic method.
3. Ensure the analysis for the dissolution rate is performed by a second dissolution-testing laboratory.
4. Microbiological examinations should be based on appropriate sections of USP and ORA's *Pharmaceutical Microbiological Manual*.[23]

[23] See https://www.fda.gov/downloads/scienceresearch/fieldscience/ucm397228.pdf.

PART V—REGULATORY/ADMINISTRATIVE STRATEGY

Inspection findings that demonstrate that an establishment is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative, or judicial actions.

The initial classification should be based on the ORA division's assessment of the seriousness of the CGMP problem.

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

All corrective actions proposed by establishments are monitored and managed collaboratively by the ORA division and OMQ. These approaches may range from shutdown of operations, recall of products, conducting of testing programs, development of new procedures, or modifications of plants and equipment to simple and immediate corrections of conditions. CDER OPQ suboffices (Office of Pharmaceutical Manufacturing Assessment (OPMA) and/or OQS) will also assist ORA divisions as requested.

If an inspection report documents that one or more of the establishment's systems are out of control, the inspection should receive an initial OAI classification. Issuing a warning letter or taking other regulatory or advisory actions pursuant to a CGMP inspection should result in the classification of all profile classes as unacceptable. Also, the inspection findings will be used as the basis for updating profile classes in eNSpect.

If there are significant concerns about the quality system, and particularly about the change management system, from an inspection that is classified as OAI at an establishment where ECs have been approved, CDER offices will collaborate to evaluate the significant findings and the firm's response for the potential impact on approved ECs. If approved ECs are impacted, CDER will notify the applicant that the reporting categories previously approved in the application for that facility will revert to reporting categories consistent with the risk-based paradigm in the regulations and as recommended in guidance.

Requests and review of records, documents, and other information from RRA activities may reveal potentially violative practices. In such cases, OMQ's evaluation of a pOAI recommendation will use approaches aligned with those discussed in this section during review of the case.

FDA laboratory tests that demonstrate effects of absent or inadequate CGMP are strong evidence for supporting regulatory actions. Such evidence development should be considered as an inspection progresses and deficiencies are found. However, the lack of violative physical samples is not a barrier to pursuing regulatory or administrative action provided that CGMP deficiencies have been well documented. Likewise, physical samples found to be in compliance are not a barrier to pursuing action under CGMP charges.

Evidence to support significant deficiencies or a trend of deficiencies within a system covered could demonstrate system failure and should result in an OAI referral to OMQ. When deciding

the type of action to recommend, the initial decision should be based on the seriousness or frequency of the problems. Examples of such problems include the following:

1. Quality System

- Pattern of failure to implement an adequate quality system
- Pattern of failure to formalize a quality risk management program
- Pattern of failure to review/approve/follow procedures
- Pattern of failure to document execution of operations as required
- Pattern of failure to review documentation
- Pattern of failure to conduct investigations and resolve discrepancies/failures/ deviations/complaints
- Pattern of failure to establish/follow an effective change management system for implementing changes across all systems/operations
- Pattern of failure to establish and maintain a state of control and facilitate needed improvements throughout a product's lifecycle.
- Pattern of failure to assess other systems to ensure compliance with CGMP requirements and internal SOPs

2. Facilities and Equipment

- Contamination with filth, objectionable microorganisms, toxic chemicals, or other drug chemicals, or a reasonable potential for contamination, with demonstrated avenues of contamination, such as airborne or through unclean equipment
- Pattern of failure to validate cleaning procedures for nondedicated equipment; lack of demonstration of effectiveness of cleaning for dedicated equipment
- Pattern of failure to document investigation of discrepancies
- Pattern of failure to establish/follow a control system for implementing changes in the equipment
- Pattern of failure to qualify equipment, including computers

3. Materials System

- Release of materials for use or distribution that do not conform to established specifications
- Pattern of failure to conduct one specific identity test for components
- Pattern of failure to document investigation of discrepancies

- Pattern of failure to establish/follow a control system for implementing changes in materials handling operations
- Lack of validation of water systems as required depending on the intended use of the water
- Lack of validation of computerized processes

4. Production System

- Pattern of failure to establish/follow a control system for implementing changes in production system operations
- Pattern of failure to document investigation of discrepancies
- Lack of process validation
- Lack of validation of computerized processes
- Pattern of incomplete or missing batch production records
- Pattern of nonconformance to established in-process controls, tests, or specifications

5. Packaging and Labeling

- Pattern of failure to establish/follow a control system for implementing changes in packaging or labeling operations
- Pattern of failure to document investigation of discrepancies
- Lack of validation of computerized processes
- Lack of control of packaging and labeling operations that may introduce a potential for mislabeling
- Lack of packaging validation

6. Laboratory System

- Pattern of failure to establish/follow a control system for implementing changes in laboratory operations
- Pattern of failure to document investigation of discrepancies
- Lack of validation of computerized or automated processes
- Pattern of inadequate sampling practices
- Lack of validated analytical methods
- Pattern of failure to follow approved analytical procedures
- Pattern of failure to follow an adequate OOS procedure

- Pattern of failure to retain raw data
- Lack of stability-indicating methods
- Pattern of failure to follow stability programs

Follow up to a warning letter or other significant regulatory action as a result of an abbreviated inspection should warrant full inspection coverage as defined in this compliance program.

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

1. References

- Code of Federal Regulations
  - 21 CFR parts 4, 210, and 211, as revised
  - Preamble to 21 CFR parts 210 and 211, General Comments (1978)
  - 21 CFR part 11, Electronic Records: Electronic Signatures
- Compliance Programs[24]
  - 7346.832—*Preapproval Inspections*
  - 7356.000—*Inspections of CDER-Led or CDRH-Led Combination Products*
  - 7356.002A—*Sterile Drug Process Inspections*
  - 7356.002E—*Compressed Medical Gases*
  - 7356.002F—*Active Pharmaceutical Ingredient (API) Process Inspection*
  - 7356.002M—*Surveillance Inspections of Protein Drug Substance Manufacturers*
  - 7356.002P—*PET CGMP Drug Process and Pre-Approval Inspections/Investigations*
  - 7356.021—*Drug Quality Reporting System (DQRS) (MedWatch Reports); NDA Field Alert Reports (FARs)*
- FD&C Act, as amended
- FDA Guidance for Industry[25]
  - *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021)
  - *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (December 2021)
  - *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)
  - *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection* (October 2014)
  - *Control of Nitrosamine Impurities in Human Drugs,* Rev. 1 (February 2021)

[24] See https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs.

[25] See https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. CDER guidance documents related to pharmaceutical quality are generally found under the following topics: pharmaceutical quality; chemistry, manufacturing, and controls; current good manufacturing practice; and microbiology.

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

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

- ICH Guidance for Industry
  - *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016)
  - *Q8(R2) Pharmaceutical Development* (November 2009)
  - *Q9 Quality Risk Management* (June 2006)
  - *Q10 Pharmaceutical Quality System* (April 2009)
  - *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and its *Annexes* (May 2021)
- Draft Guidance for Industry[26]
  - *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)

- Inspection Guides[27]
  - Computerized Systems in Drug Establishments
  - Dosage Form Drug Manufacturers CGMPs
  - Pharmaceutical Quality Control Labs
  - High Purity Water Systems
  - Validation of Cleaning Processes
- *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept Of Operations*, https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/UCM574362.pdf

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

[27] See https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-guides.

- *Investigations Operations Manual,* https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/investigations-operations-manual
- Manual of Compliance Policy Guides, Chapter 4—Human Drugs, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/manual-compliance-policy-guides/chapter-4-human-drugs
- Pharmaceutical Inspection Co-operation Scheme (PIC/S) recommendation PI 054-1 *How To Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in Relation to Risk-Based Change Management*, https://picscheme.org/docview/4294
- *Pharmaceutical Microbiological Manual,* ORA.007, https://www.fda.gov/downloads/scienceresearch/fieldscience/ucm397228.pdf
- *Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals,* https://www.fda.gov/media/157432/download
- *Regulatory Procedures Manual,* https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual

2. Attachments

Attachment A: Remote Regulatory Assessments

Attachment B: Indicators of an Advanced Quality System

3. Contacts

A. Office of Regulatory Affairs

For technical questions concerning inspections, contact:

Office of Medical Products and Tobacco Operations (OMPTO)
Division of Medical Products and Tobacco Program Operations (DMPTPO)
301-796-0358
ORAHQDrugInspectionPOC@fda.hhs.gov

Office of Regulatory Science/Office of Medical Products, Tobacco, and Specialty Laboratory Operations (OMPTSLO)
ORSOMPSLOProgramCoordinators@fda.hhs.gov

B. Center for Drug Evaluation and Research

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

Postapproval Change Management Questions
For postapproval change management questions related to the impact and reporting of a change on an approved product, whether it should have been reported, or whether it was submitted appropriately (e.g., supplement vs. annual report), please send an email to the following address and it will be triaged to the appropriate CDER assessor:
CDER-OPQ-OPMA-Policy@fda.hhs.gov
cc: CDERBIOTECHINSPECT@fda.hhs.gov (biological products)

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

Labeling Requirements and Policies
Office of Unapproved Drugs and Labeling Compliance, see FDA's SharePoint site for contacts [FDA Organizations | CDER | CDER Offices | Office of Compliance | Office of Unapproved Drugs and Labeling Compliance]

Registration and Drug Listing Requirements
CDER Office of Compliance, see FDA's SharePoint site for contacts [FDA Organizations | CDER | Office of Communications | "CDER: Who's the Lead" link (on resulting page, scroll down to the Drug Registration and Listing entry under Office of Compliance)]

4. Acronyms

API:	active pharmaceutical ingredient
BPDR:	biological product defect report
CAPA:	corrective action and preventive action
CDER:	Center for Drug Evaluation and Research
CGMP:	current good manufacturing practice
CMS:	Compliance Management System
DQRS:	Drug Quality Reporting System
EC:	established condition
EIR:	establishment inspection report
FAR:	field alert report
FD&C Act:	Federal Food, Drug, and Cosmetic Act

FDASIA:	Food and Drug Administration Safety and Innovation Act
FMD:	Field Management Directive
ICH:	International Council for Harmonisation
IOM:	Investigations Operations Manual
MRA:	mutual recognition agreement
NAI:	No Action Indicated
NDA:	new drug application
OAI:	Official Action Indicated
OC:	Office of Compliance
OMPTSLO:	Office of Medical Products, Tobacco, and Specialty Laboratory Operations
OMQ:	Office of Manufacturing Quality
OOS:	out-of-specification
OPMA:	Office of Pharmaceutical Manufacturing Assessment
OPQ:	Office of Pharmaceutical Quality
OQS:	Office of Quality Surveillance
ORA:	Office of Regulatory Affairs
ORS:	Office of Regulatory Science
PAC:	product/assignment code
PAM:	preapproval program manager
PET:	positron emission tomography
PLCM:	product lifecycle management
pOAI:	potential Official Action Indicated
PQS:	pharmaceutical quality system
RRA:	remote regulatory assessments
RIE:	remote interactive evaluation
SOP:	standard operating procedure
USP:	United States Pharmacopeia
VAI:	Voluntary Action Indicated

PART VII—CDER AND ORA RESPONSIBILITIES OVERVIEW

CDER and ORA redefined their roles and responsibilities with regard to application review and inspections of human drugs facilities under the concept of operations *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept Of Operations* (ConOps).[28] This ConOps operating model applies to preapproval, postapproval, surveillance, and for-cause inspections. The roles and responsibilities for surveillance and surveillance-related for-cause inspections subject to this compliance program are summarized below.

1. Surveillance Inspection Responsibilities

OQS uses a risk-based site selection model to identify establishments for inspection and prepares an up-to-date site dossier for each of the identified establishments in advance of a scheduled surveillance inspection. ORA schedules surveillance inspections for individual sites. ORA leads surveillance establishment inspections with CDER participation, when requested by ORA. ORA then conducts an on-site inspection based on this compliance program and compliance program 7356.002M, as appropriate, and quality information summarized in the site dossier.

If the initial classification is OAI, the responsible ORA division provides a written classification analysis, including the electronic documents, to OMQ within 45 calendar days of closing the inspection. OMQ makes a final classification with input from the Office of the Chief Counsel, if needed, and issues a decisional letter in the following 45 calendar days (90 calendar days following the inspection closing). If an inspection is classified as final OAI, OMQ, solely or in collaboration with ORA, takes an appropriate action within 90 calendar days of the decisional letter. If OMQ determines that an advisory or enforcement action is not warranted, ORA is notified of the change in classification. OMQ will then issue an FMD 145 decisional letter no later than 90 calendar days following the inspection closing.

If the establishment inspection results in an ORA recommendation for a No Action Indicated (NAI) or Voluntary Action Indicated (VAI) classification and no further action is recommended, ORA issues an FMD 145 decisional letter within 90 calendar days following the inspection closing.

2. For-Cause Inspection Responsibilities

Requests for for-cause inspections can be initiated by ORA, OPMA, OQS, or OC. Once the initiating office determines a for-cause inspection is warranted, the office prepares an assignment that sets forth the areas of required coverage, which may or may not include surveillance program coverage. If required, ORA approves the assignment as per FMD 17 and schedules the inspection. ORA leads the inspection, and CDER participates when appropriate.

[28] See https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/UCM574362.pdf.

ORA or CDER will not issue an FMD 145 decisional letter without the concurrence of the initiating office. For-cause inspections that result in surveillance program coverage and are initially classified OAI will receive final classification from OMQ 90 days after the close of the inspection; OMQ involves other offices (e.g., ORA, OPMA, OQS) as appropriate, based on the inspection findings. In addition, the office that initiates the for-cause inspection assignment completes the final assessment 90 days after the close of the inspection, involving other offices (e.g., ORA, OPMA, OQS, OC) as appropriate. Any follow-up actions are completed by CDER within 6 months after the inspection.

ATTACHMENT A: REMOTE REGULATORY ASSESSMENTS

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

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

The following RRAs, along with applicable FDA policies, may be used to help meet the objectives of this compliance program to determine whether the establishment meets CGMP requirements.

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, the use of this authority helps strengthen FDA's surveillance program and improve the overall effectiveness of the drug inspection program. The records received from an establishment can be used to help assess an establishment's compliance with current good manufacturing practice, support regulatory decisions, inform inspection planning (e.g., a risk-based inspection schedule), and prepare for a scheduled inspection (e.g., inspection coverage). The use of 704(a)(4) authority does not prevent an FDA investigator from requesting records or other information on inspection. During an inspection, FDA may collect copies of previously received documents and other documents not previously requested.

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

2. Remote Interactive Evaluation (Voluntary RRA)

A remote interactive evaluation (RIE) is an evaluation of a firm's compliance with regulations that a firm participates in voluntarily.[2] 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 establishments 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, the use of RIEs helps strengthen FDA's surveillance program and improve the overall effectiveness of the drug inspection program. Information evaluated from an RIE may be used to help assess an establishment's compliance with current good manufacturing practice, support regulatory decisions, inform inspection planning (e.g., a risk-based inspection schedule), and prepare for a scheduled inspection (e.g., inspection coverage).

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

ATTACHMENT B: EXAMPLES OF INDICATORS OF AN ADVANCED QUALITY SYSTEM

Manufacturers can demonstrate practices that are indicative of mature quality practices that, if effectively implemented, provide the foundation for exceeding current good manufacturing practice (CGMP) requirements. Examples may include a steadfast focus on implementing continual improvements, using the latest innovations to enhance control,[1] and creating a culture of quality where leadership demonstrates a commitment to quality and promotes employee engagement and empowerment. For manufacturers with a more advanced quality system, FDA may exercise a more flexible regulatory approach, leading toward the goal of producing high-quality drug products without extensive regulatory oversight.[2]

During an inspection, investigators may assess quality management practices to gain insight into an establishment's processes and continual system improvements. The areas below are examples of indicators of an advanced quality system, some of which may be evaluated during an inspection.

- **Management Responsibility**
  - Communication and reward system for employees to bring quality issues to the attention of management
  - Monitoring of external regulatory and business environments to identify unexpected risks to quality
  - Increased levels of personnel understanding, ownership, and engagement that create company-wide quality commitment
  - All personnel trained on the impact of poor quality on the patient
- **Investigations**
  - Effective use of standardized tools (e.g., FMEA, DOE, 5 Whys, fishbone diagram)[3] to determine a potential root cause
- **Corrective Actions and Preventive Actions**
  - Routine production and laboratory "shop floor" meetings (e.g., weekly) to collect employee feedback, reduce operational risks, and ensure initiation of corrective actions and preventive actions

[1] The term *innovation* is defined as the introduction of new technologies or methodologies. See ICH Q10.

[2] See the International Council for Harmonisation guidances for industry *Q10 Pharmaceutical Quality System* and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and the Office of Pharmaceutical Quality's white paper *Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals*.

[3] FMEA=failure mode and effects analysis; DOE=design of experiments.

- **Supply Chain and Contracted Service Management**
  - Consistently meeting planned time frames for product delivery to the customer or internal stock because of high manufacturing robustness (i.e., avoiding delays caused by manufacturing quality problems)
  - Active solicitation and analysis of customer feedback (beyond solely complaints) related to quality and delivery
- **Training Program**
  - Extensive staff training on Six Sigma and/or other advanced quality assurance tools to improve process capability
- **Quality Oversight**
  - Electronic systems that use analytics to optimize implementation of knowledge management related to products, processes, and components
  - Continual improvement program to optimize quality indicator metrics
- **Process Parameters, Product Quality Monitoring, and Annual Product Review**
  - Programs to improve manufacturing processes by adopting the latest beneficial innovations and technologies
  - Use of visuals throughout the establishment to indicate quality performance status