CHAPTER 56: DRUG QUALITY ASSURANCE

SUBJECT: DRUG MANUFACTURING INSPECTIONS Revision Note: Program revised to add potential OAI reporting responsibilities and to align with the CDER and ORA agreement, Concept of Operations for Facility Evaluation and Inspection.	**IMPLEMENTATION DATE** 10/31/2017 **COMPLETION DATE**

DATA REPORTING

PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
All Human Drugs Industry codes: 50, 54-56, 59, 60-66	**Domestic/Foreign surveillance inspections covered under this program, 7356.002, include inspection of any facility that does not have a specific program:**

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

Report coverage of the surveillance programs specified below under the following PACs:

PAC	Type	Subject
56002A	Full	DPI/Small Volume Parenterals (CPGM: Sterile Drug Process Inspections)
56002I	Abbreviated	DPI/Small Volume Parenterals (CPGM: Sterile Drug Process Inspections)
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
56002P	Full	Drug Process Inspections - PET Domestic (CPGM: PET CGMP Drug Process and Pre- Approval Inspections/Investigations)
56002Q	Abbreviated	Drug Process Inspections - PET Domestic (CPGM: PET CGMP Drug Process and Pre- Approval Inspections/Investigations)

Note: The following three surveillance programs are reported under single PACs; there are no full or abbreviated specific PACs:

PAC	Subject
56002E	DPI/Medical Gas Manufacturers (CPGM: Compressed Medical Gases)
56002M	DPI/Therapeutic Biological Product Inspections (CPGM: Inspections of Licensed Biological Therapeutic Drug Products)
56002S	Drug Process Inspections - Biosimilars
56843	Post Approval Inspections/Investigations

(Continued on next page)

FIELD REPORTING REQUIREMENTS

The 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 Office of Regulatory Affairs (ORA) and CDER (Center for Drug Evaluation and Research).

ORA divisions should, as soon as practical, report significant inspection issues into FACTS, as per the Investigations Operations Manual (IOM). For inspections initially classified as Official Action Indicated (OAI) due to failure to comply with Current Good Manufacturing Practice (CGMP), submit the written classification analysis and electronic documents to CDER's Office of Compliance (OC), Office of Manufacturing Quality (OMQ) for evaluation via CMS.[1]

ORA divisions (e.g., Pre-Approval Program Managers (PAMs)) are responsible for timely reporting of potential OAI (pOAI) alerts into Panorama[2] as per the current procedures.[3] The PAM should take into consideration the following when entering a pOAI alert into Panorama:

1. For surveillance 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 pre-approval coverage are provided during the same inspection:
   - Do not enter a pOAI alert for significant application-specific pre-approval issues which do not impact marketed product; refer to CPGM 7346.832.
   - Do enter a pOAI alert for significant surveillance issues (see point 1).

The 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 CDER/OC/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 you obtain information pertaining to inadequate adverse drug experience (ADE) reporting, unapproved drug issues, or post-approval reporting violations (failing to submit application supplements, Field Alert Reports (FARs), etc.), report in accordance with directions

[1] For further information see Part V Regulatory/Administrative Strategy

[2] PANORMA: CDER Time Reporting and Workflow Management System

[3] Refer to Panorama Step-By-Step guides for creating, editing and closing pOAI alerts.

[4] Guidance for Industry Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection. See https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm360484.pdf

provided in the applicable compliance programs and under separate captions in the EIR. Data system information about these inspectional activities should be reported under separate Program Assignment Codes (PACs). Expansion of coverage under these programs into a CGMP inspection 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 program governing ORA and CDER interactions supersede the instructions in the other programs for the 5600 PACs (e.g., 7356.002A, 7356.002F, 7356.002P), with the exception of inspections reported under PAC 56843.

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 own compliance programs. API inspections per CPGM 7356.002F are conducted to verify adherence to section 501(a)(2)(B) of the Food, Drug, and Cosmetic Act using ICH Q7 as a guideline. PET inspections per CPGM 7356.002P are conducted to verify adherence to 21 CFR Part 212.

PART I - BACKGROUND

Until 2012, FDA was required to inspect domestic establishments 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),[5] which amended the FD&C Act section 510(h), 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 the agency formalized its process for selecting establishments for inspection based on risk factors specified by section 510(h) of the Act.

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

FDA expects that establishments that comply with CGMP are likely to operate in a state of control and consistently manufacture drug products of acceptable quality. FDA will use information gathered from surveillance inspections to, among other things, make assessments about manufacturing facilities listed in pending drug applications.

The inspectional guidance in this program is 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 firms and inspections. It also provides guidance for conducting for-cause inspections as appropriate (see page 9 under PROGRAM MANAGEMENT INSTRUCTIONS).

[5] Food and Drug Administration Safety and Innovation Act (FDASIA), see https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf, page 1067.

PART II- IMPLEMENTATION

OBJECTIVES

The goal of this 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 program, inspections, investigations, sample collections, sample analyses, and regulatory or administrative follow-up are made in order to identify quality problems and adverse trends at establishments, so that FDA can develop strategies to mitigate them. The objectives of this program are:

- to determine whether inspected firms are operating in compliance with applicable CGMP requirements, and if not, to provide the evidence for actions to prevent adulterated products from entering the market; as appropriate, to remove adulterated products from the market, and to take action against persons responsible;

- to provide an assessment of firms' conformance to CGMP requirements for Agency decisions;

- to provide input to firms during inspections to improve their compliance with regulations; and,

- to better understand current practices in drug manufacturing for the purpose of updating the CGMP requirements, regulatory policy, and guidance documents.

STRATEGY

A. Inspection of Manufacturing Establishments (includes repackaging, contract labs, etc.)

Drug products are manufactured using many physical operations that bring together components, and 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 firm will produce drugs that are safe, have the identity and strength, and meet the quality and purity characteristics as intended.

This program applies to all manufacturing operations at the establishment.

It is not practical for FDA to audit every aspect of CGMP in every manufacturing facility 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 FACTS, for each inspection, provides the most broadly resource-efficient approach. This 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 firm. 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 firm. For example, the way a firm handles "materials" (i.e., receipt, sampling, testing, acceptance, etc.), should be the same for all profile classes. An inspection does not have to include each 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 SOP use, charge-in of components, equipment identification, in- process sampling and testing which 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 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.

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

C. **A 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 211 CGMP regulations. Every effort was made to group whole subchapters together in a rational set of six systems which 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 above 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 assures overall compliance with CGMPs and internal procedures and specifications. This system includes the quality control unit and all of its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports, etc.). It includes all product defect evaluations and evaluation of returned and salvaged drug products. See the CGMP regulations, 21 CFR 211 Subparts B, E, F, G, I, J, and K.

2) **Facilities and Equipment System**. This system includes the measures and activities which provide an appropriate physical environment and resources used in the production of the drugs or drug products. It includes:

    a) Buildings and facilities along with maintenance;
    b) Equipment qualifications (installation and operation); equipment calibration and preventative 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; and,
    c) Utilities that are not intended to be incorporated into the product such a HVAC, compressed gases, steam and water systems.

    See the CGMP regulations, 21 CFR 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, drug storage, distribution controls, and records. See the CGMP regulations, 21 CFR 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 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 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 211 Subparts B, I, J, and K.

As this program approach is implemented, the experience gained will be reviewed to make modifications to the system definitions and organization as needed.

PROGRAM MANAGEMENT INSTRUCTIONS

A. Definitions

1. Surveillance Inspections

The Full Inspection Option

The Full Inspection Option is a surveillance inspection meant to provide a broad and in-depth evaluation of the firm's conformance with CGMP requirements. A Full Inspection may change to an Abbreviated Inspection Option 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 which includes the responsibility for the annual product reviews).

The Abbreviated Inspection Option

The Abbreviated Inspection Option is a surveillance inspection meant to provide an efficient updated evaluation of a firm's conformance with CGMP requirements. The abbreviated inspection will provide documentation for continuing a firm in a satisfactory CGMP compliance status. Generally this will be done when a firm 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 firm since the last inspection. See Part III, Section B.2. 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 which includes the responsibility for the annual product reviews). 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 firms participate in a limited part of the production of a drug or drug product, e.g., a contract laboratory. Such firms may employ only two of the systems defined. In these cases the inspection of the two systems will comprise inspection of the entire firm and will be considered the Full Inspection Option.

Selecting Systems for Coverage

The selection of the system(s) for coverage will be made by the ORA division based on the firm's specific operation, history of previous coverage, history of compliance, or other priorities determined by the ORA division.

2. For-Cause Inspections

A for-cause inspection is defined to include: (i) Follow-up compliance inspections performed to verify corrective actions after a regulatory action has been taken; (ii) inspections performed in response to specific events or information (Field Alert Reports (FARs), Biological Product Defect Reports (BPDRs), industry complaints, recalls, and other indicators of defective products, etc.) that bring into question the compliance and/or quality of a manufacturing practice, facility, process, or drug.

For-cause inspections that are to be initiated and reported under this program include follow-up compliance inspections performed to verify corrective actions after a regulatory action has been taken. Follow-up 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 the FDA-483 for a previous inspection. The decision to add systems coverage is made on case-by-case basis.

For-cause inspections in response to FARs defect reports are to be initiated and performed under CPGM 7356.021.

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 firm is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of Sections 501(a)(2)(B) of the Act and the portions of the CGMP regulations that pertain to their systems. A firm in a state of control produces finished drug products for which there is an adequate level of assurance of quality, strength, identity and purity.

A firm 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 system(s) cannot be adequately assured. 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 out of control systems/firm.

4. Drug Process

A drug process is a related series of operations which 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, packing, labeling, testing, etc.

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 maintain profiles or other monitoring systems. The ORA division is responsible for determining the depth of coverage given to each drug firm. The depth of inspection coverage should be determined by the firm's compliance history, the manufacturing technology employed, and the characteristics of the products. CGMP inspectional coverage shall be sufficient to assess the state of control and compliance for each firm.

In advance of a scheduled Surveillance Inspection, the Office of Quality Surveillance (OQS) in the Office of Pharmaceutical Quality (OPQ)/CDER prepares an up-to-date site dossier which includes but is not limited to, quality information on facility inspection history, recalls, shortages, customer complaints, foreign regulator inspection outcomes, information on submitted Field Alert Reports (FARs) or Biological Product Defect Reports (BPDRs), submitted quality metrics data if available, and a listing of all products manufactured at the site. When a system is inspected, the inspection of that system may be considered applicable to all products which 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 firm's overall abilities in manufacturing within CGMP requirements.

Products posing special challenges, such as low dose products, narrow therapeutic range drugs, combination products,[6] 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 section 5.5.1.2 – Inspectional Approach[7]).

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 a firm 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 screen of the FACTS EIR coversheet that is used to record profile/class determinations. Normally, an inspection under this risk-based systems approach will result in all profile classes being updated.

[6] Combination products are subject to the CGMP requirements outlined in 21 CFR Part 4. See the FDA Guidance for Industry and Staff: Current Good Manufacturing Practice Requirements for Combination Products for more information at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf.

[7] Investigations Operations Manual, https://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM150576.pdf

PART III – INSPECTIONAL

INVESTIGATIONAL OPERATIONS

A. General

Review and use the CGMP regulations for Finished Pharmaceuticals (21 CFR 210 and 211) and related guidance for industry to evaluate manufacturing processes.

The investigator should conduct inspections according to the STRATEGY section in Part II of this compliance program. Recognizing that drug firms vary greatly in size and scope, and manufacturing systems are more or less sophisticated, the approach to inspecting each firm should be carefully planned. For example, it may be more appropriate to review the Quality System thoroughly before entering production areas in some firms; in others, the Quality System review should take place concurrently with inspection of another system or systems selected for coverage. The complexity and variability necessitate a flexible inspection approach; one which allows the investigator to choose the inspection focus and depth appropriate for a specific firm, but also one which directs the performance and reporting on the inspection within a framework which will provide for a uniform level of CGMP assessment. Furthermore, this inspection approach will provide for fast communication and evaluation of findings.

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, etc. CGMP requirements apply to the manufacture of all human drugs, which include prescription and non-prescription drug products, drug products that are the subject of pending applications, drug products used in clinical trials, as well as products not requiring approval.

Active Pharmaceutical Ingredient (API) and Positron Emission Tomography (PET) drug inspections are performed to verify conformance with different quality standards than 21 CFR 210 and 211 and have their own compliance programs. API inspections are conducted under CPGM 7356.002F, which employs ICH Q7 as a quality standard, and establishes compliance to the statutory requirement of the section 501(a)(2)(B) of the FD&C Act. Firms that follow ICH Q7 generally will be considered to comply with the statutory requirement. PET inspections under CPGM 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 to Industry 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 the FDA-483, when issued, should be specific and contain only significant items. For this program, inspection observations should be organized under separate captions by the systems defined in this 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 the FDA-483 and in the text of the EIR, reference the applicability to other systems where appropriate. This is being done to accommodate the structure of eNSpect which allows individual citation once per FDA-483. Refrain from using unsubstantiated conclusions. Do not use the term "inadequate" without explaining why and how. Refer to policy in the 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 as attachments to this program, or in requests for inspection, assignments, etc.

B. Inspection Approaches

This program provides two surveillance inspectional options, Full Inspection Option and the Abbreviated Inspection Option . See the definitions of the inspection options in Part II of this program.

1. Selecting the Full Inspection Option. The Full Inspection Option will include inspection of at least four of the systems listed in Part II Strategy, one of which must be the Quality System.

a) 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 the Abbreviated Inspection Option, with **ORA division concurrence**.

For efficient use of FDA resources, before scheduling the surveillance coverage of the newly registered establishment, the ORA division should consult with CDER to determine whether it is listed in any pending application and also needs a pre-approval inspection.

b) Select the Full Inspection Option when the firm has a history of fluctuating into and out of compliance. To determine if the firm meets this criterion, the ORA division should utilize all information at its disposal, such as inspection results, results of sample analyses, complaints, DQRS and BPDR reports, recalls, etc. and the compliance actions resulting from them or from past inspections.

c) Evaluate if 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:

1) New potential for cross-contamination arising through change in process or product line.

2) Use of new technology requiring new expertise, significant new equipment, or new facilities.

d) A Full Inspection may also be conducted on a surveillance basis at the ORA division's discretion.

2. **Selecting the Abbreviated Inspection Option.** The Abbreviated Inspection Option normally will include 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

   a) This option involves an inspection of the manufacturer to maintain surveillance over the firm's activities and to provide input to the firm on maintaining and improving the CGMP level of assurance of quality of its products.

   b) A Full Inspection may change to the Abbreviated Inspection option, with ORA division concurrence, based on inspection history.

   c) Abbreviated Inspection coverage may be changed to the Full Inspection Option at the discretion of the ORA division.

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 firm'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 case-by-case basis at the discretion of the ORA division prior to or during the inspection.

C. System Inspection Coverage

QUALITY SYSTEM

Assessment of the Quality System is two-phased. The first phase is to evaluate whether the Quality Control Unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated recordkeeping systems. The second phase is to assess the data collected to identify quality problems which may link to other major systems for inspectional coverage.

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm'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 major systems that would warrant expansion of coverage.
All areas under this system should be covered; however, the depth of coverage may vary depending upon inspectional findings.

- Product reviews: at least annually; should include information from areas listed below as appropriate; batches reviewed, for each product, are representative of all batches manufactured; trends are identified; refer to 21 CFR 211.180(e)
- Complaint reviews (quality and medical): documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- Discrepancy and failure investigations related to manufacturing and testing: documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- Change Control: documented; evaluated; approved; need for revalidation assessed
- Product Improvement Projects: for marketed products
- Reprocess/Rework: evaluation, review and approval; impact on validation and stability
- Returns/Salvages: assessment; investigation expanded where warranted; disposition
- Rejects: investigation expanded where warranted; corrective action where appropriate
- Stability Failures: investigation expanded where warranted; need for field alerts evaluated; disposition
- Quarantine products
- Validation: status of required validation/revalidation (e.g., computer, manufacturing process, laboratory methods)
- Training/qualification of employees in quality control unit functions

FACILITIES AND EQUIPMENT SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. 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 upon inspectional findings.

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 firm 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

2. Equipment

- equipment installation and operational qualification where appropriate
- adequacy of equipment design, size, and location
- equipment surfaces should not be reactive, additive, or absorptive
- appropriate use of equipment operations substances, (lubricants, coolants, refrigerants, etc.) contacting products/containers
- cleaning procedures and cleaning validation for re-usable or multi-product equipment
- controls to prevent contamination, particularly with any pesticides or any other toxic materials, or other drug or non-drug chemicals
- qualification, calibration and maintenance of storage equipment, such as refrigerators and freezers for ensuring that standards, raw materials, reagents, etc. 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 any unexpected discrepancy

MATERIALS SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm'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 upon inspectional findings.

- training/qualification of personnel
- identification of components, containers, closures
- inventory of components, containers, 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 is conducted on each lot of each component
- a visual identification is conducted on each lot of containers and closures
- testing or validation of supplier's test results for components, containers and closures
- rejection of any component, container, closure not meeting acceptance requirements
- Investigate fully the firm's procedures for verification of the source of components.
- appropriate retesting/reexamination of components, containers, closures
- first in – first out use of components, containers, closures
- quarantine of rejected materials
- water and process gas supply, design, maintenance, validation and operation
- containers and closures should not be 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 any unexpected discrepancy

PRODUCTION SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm'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 upon 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%
- identification of equipment with contents, and where appropriate phase of manufacturing and/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
- change control; the need for revalidation evaluated
- documented investigation into any unexpected discrepancy

PACKAGING AND LABELING SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products, but 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 upon 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 which are similar in size, shape, and color for different products
- finished product cut labels for immediate containers which 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 21CFR 211.132 and Compliance Policy Guide, Sec. 450.500)[8]
- validation of packaging and labeling operations including validation and security of computerized processes
- documented investigation into any unexpected discrepancy

LABORATORY CONTROL SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only 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 upon 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., GC or HPLC)

[8] CPG Sec. 450.500 Tamper-Resistant Packaging Requirements for Certain Over-the-Counter Human Drug Products. See https://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074391.htm

- specifications, standards, and representative sampling plans
- adherence to the written methods of analysis
- validation/verification of analytical methods
- control system for implementing changes in laboratory operations
- required testing is performed on the correct samples
- documented investigation into any unexpected discrepancy
- complete analytical records from all 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 which 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

D. **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 program coordinator (chemistry, microbiology) in ORS/OMPTSLO identified in CONTACTS for guidance and types of samples (in process or finished product) to be collected and for 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 and/or documentary samples of products which 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.

E. **Inspection Teams**

An inspection team (see IOM section 5.1.2.5 – Team Inspections) composed of experts from within the Division, other ORA divisions, or Headquarters is encouraged when it provides needed expertise and experience. Contact ORA/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/Office of Regulatory Science. Each inspection team member is responsible for preparing for, executing, and documenting the inspection, including contributing to the establishment inspection report, which documents the items covered during the inspection, within established timeframes.

F. **Reporting**

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

The investigator will utilize IOM Subchapter 5.10 – 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

ANALYZING LABORATORIES

The types of analyses that may be performed under this 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

SERVICING LABORATORY

Contact (email) ORAHQ ORS Management <ORAORSMANAGEMENT@fda.hhs.gov> for servicing laboratory(s) for all chemical and microbiological testing. When contacting ORS for servicing laboratories provide product description, lots to be tested, analyses to be performed, and 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, correctly identify laboratories and should not be used for selecting servicing laboratories under this program.]

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 must be confirmed by a mass spectroscopic method.

3. Check Analysis for dissolution rate must be performed by a second dissolution-testing laboratory.

4. Microbiological examinations should be based on appropriate sections of USP and Pharmaceutical Microbiological Manual (PMM).[9]

[9] Pharmaceutical Microbiological Manual (PMM), ORA.007,
See https://www.fda.gov/downloads/scienceresearch/fieldscience/ucm397228.pdf

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative, and/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 firm that have been taken or will be taken and when. All deficiencies noted in inspections/audits under this program must be addressed by stating the firm'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 firms are monitored and managed collaboratively by the ORA division and OMQ. These approaches may range from shut down of operations, recall of products, conducting testing programs, development of new procedures, modifications of plants and equipment, to simple immediate corrections of conditions. CDER OPQ sub-offices (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 systems at the establishment is/are out of control, the inspection should receive an initial OAI classification. Issuance of a Warning Letter or taking other regulatory or advisory actions pursuant to a surveillance 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 FACTS.

FDA laboratory tests that demonstrate effects of absent or inadequate current good manufacturing practice 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 and/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 and/or a trend of deficiencies within a system covered could demonstrate the failure of a system and should result an OAI referral to OMQ. When deciding the type of action to recommend, the initial decision should be based on the seriousness and/or the frequency of the problems. Examples of such problems include the following:

Quality System:

1) Pattern of failure to review/approve procedures

2) Pattern of failure to document execution of operations as required

3) Pattern of failure to review documentation

4) Pattern of failure to conduct investigations and resolve discrepancies/failures/ deviations/complaints

5) Pattern of failure to assess other systems to assure compliance with CGMP and SOPs

Facilities and Equipment

1) 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

2) Pattern of failure to validate cleaning procedures for non-dedicated equipment; Lack of demonstration of effectiveness of cleaning for dedicated equipment

3) Pattern of failure to document investigation of discrepancies

4) Pattern of failure to establish/follow a control system for implementing changes in the equipment

5) Pattern of failure to qualify equipment, including computers

Materials System

1) Release of materials for use or distribution that do not conform to established specifications

2) Pattern of failure to conduct one specific identity test for components

3) Pattern of failure to document investigation of discrepancies

4) Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations

5) Lack of validation of water systems as required depending upon the intended use of the water

6) Lack of validation of computerized processes

Production System

1) Pattern of failure to establish/follow a control system for implementing changes in the production system operations

2) Pattern of failure to document investigation of discrepancies

3) Lack of process validation

4) Lack of validation of computerized processes

5) Pattern of incomplete or missing batch production records

6) Pattern of nonconformance to established in-process controls, tests, and/or specifications

Packaging and Labeling

1) Pattern of failure to establish/follow a control system for implementing changes in the packaging and/or labeling operations

2) Pattern of failure to document investigation of discrepancies

3) Lack of validation of computerized processes

4) Lack of control of packaging and labeling operations that may introduce a potential for mislabeling

5) Lack of packaging validation

Laboratory System

1) Pattern of failure to establish/follow a control system for implementing changes in the laboratory operations

2) Pattern of failure to document investigation of discrepancies

3) Lack of validation of computerized and/or automated processes

4) Pattern of inadequate sampling practices

5) Lack of validated analytical methods

6) Pattern of failure to follow approved analytical procedures

7) Pattern of failure to follow an adequate OOS procedure

8) Pattern of failure to retain raw data

9) Lack of stability indicating methods

10) 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 program.

PART VI – REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

REFERENCES

- Federal Food, Drug, and Cosmetic Act, as amended
- Code of Federal Regulations, Title 21, Parts 4, 210 and 211, as revised
- Preamble to Code of Federal Regulations, Title 21, Parts 210 and 211 General Comments (1978)
- 21 CFR Part 11 Electronic Records: Electronic Signatures
- Inspection Operations Manual
- Regulatory Procedures Manual
- Compliance Policy Guides Manual, Chapter 4 Human Drugs
- Guidance for Industry[10]
    - Pharmaceutical Quality/CMC[11]
    - Pharmaceutical Quality/Manufacturing Standards (CGMP)[12]
    - Pharmaceutical Quality/Microbiology[13]
    - Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection
    - Current Good Manufacturing Practice Requirements for Combination Products
    - ICH Guidelines[14]
        - Q8(R2) Pharmaceutical Development
        - Q9 Quality Risk Management
        - Q10 Pharmaceutical Quality System
- Inspection Guides[15]
    - Computerized Systems in Drug Establishments
    - Guide to Inspections of Dosage Form Drug Manufacturers-CGMPs
    - Guide to Inspections of Lyophilization of Parenterals
    - Guide to Inspections of Pharmaceutical Quality Control Laboratories
    - Guide to Inspections of High Purity Water Systems
    - Guide to Inspections of Validation of Cleaning Processes

[10] See https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
[11] See https://www.fda.gov/drugs/pharmaceutical-quality-resources/guidances-and-manuals-pharmaceutical-quality
[12] See https://www.fda.gov/drugs/pharmaceutical-quality-resources/guidances-and-manuals-pharmaceutical-quality
[13] See https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064983.htm
[14] See https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/ich-guidance-documents
[15] See https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-guides

ATTACHMENTS

Attachments to the Drug Process Inspection program may be issued for certain industries, dosage forms, and processes with known problems or unique drug processes. These attachments will contain the guidance needed to perform these specialized inspections.

Some of the attachments to be issued with this program may include reporting requirements specifically designed to obtain industry-wide information on certain practices to permit evaluation of the adequacy of FDA's regulatory efforts.

Attachments and/or reporting requirements will be periodically reviewed and evaluated and deleted from the program when they are no longer needed.

CONTACTS

For technical questions concerning inspections contact: Office of Regulatory Affairs (ORA)

Office of Medical Products and Tobacco Operations (OMPTO)

Division of Medical Products and Tobacco Program Operations (DMPTPO) Telephone number: 301-796-0358
Email: ORAHQDrugInspectionPOC@fda.hhs.gov

Office of Regulatory Science/
Office of Medical Products, Tobacco & Specialty Laboratory Operations (OMPTSLO)

Shari Kahn (Chemistry) 301-796-8154, shari.kahn@fda.hhs.gov
Angele Smith (Microbiology) 301-796-4200, Angele.smith@fda.hhs.gov

Center for Drug Evaluation and Research

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

OPQPolicy@fda.hhs.gov

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:

CDER OMQ Compliance Policy
CDEROMQCompliance@fda.hhs.gov

Labeling Requirements and Policies

Office of Unapproved Drugs and Labeling Compliance, see intranet home page for contacts
[CDER | Office of Compliance | Office of Unapproved Drugs and Labeling Compliance]

Registration and Drug Listing Requirements

CDER Office of Compliance, see "CDER: Who's the Lead" intranet page for contacts
[CDER | Office of Communications | CDER: Who's the Lead]

PART VII - CDER AND ORA RESPONSIBILITIES OVERVIEW

CDER and ORA recently redefined their roles and responsibilities with regard to application review and inspections of human drugs facilities under the concept of operations (ConOps).[16] This ConOps operating model applies to pre- and post-approval, surveillance, and for-cause inspections. The roles and responsibilities for surveillance and surveillance related for-cause inspections subject to this Program 7356.002 are summarized below.

Surveillance Inspection Responsibilities:

OQS uses a risk-based site selection model to identify facilities for inspection, and prepares an up-to-date site dossier for each of the identified facilities in advance of a scheduled surveillance inspection. ORA schedules surveillance inspections for individual sites. ORA leads surveillance facility inspections with CDER participation, when requested by ORA. ORA then conducts an on-site inspection based on the Surveillance Compliance Program and quality information summarized in the site dossier.

If the intial 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 facility inspection results in an ORA recommendation for an NAI or VAI classification and no further action is recommended, ORA issues an FMD-145/decisional letter within 90 calendar days following the inspection closing.

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, and performs the inspections with CDER participation, when appropriate.

ORA or CDER will not issue an FMD-145 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 in 90 days following the close of the inspection; OMQ involves other offices (e.g., ORA, OPMA, OQS, OC) as appropriate, based on the inspection findings. In addition, the office that initiates the for-cause inspection assignment completes the final assessment in 90 days following 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 post-inspection.

[16] Integration Of FDA Facility Evaluation And Inspection Program For Human Drugs: A Concept Of Operations (ConOps), see https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/UCM574362.pdf