CHAPTER 56—DRUG QUALITY ASSURANCE

SUBJECT: Outsourcing Facility Inspections	IMPLEMENTATION DATE: 02/15/2025
DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
All Human Drugs Industry Codes: 54–56, 60–66	**PAC** **Subject** 56040 Outsourcing Facility Inspection 56040A Abbreviated Outsourcing Facility Inspection

FIELD REPORTING REQUIREMENTS:

1. Establishment Inspection Reports (EIRs) are to be created and filed electronically using the specific module in eNSpect or replacement system that is accessible to both the Office of Inspections and Investigations (OII) and the Center for Drug Evaluation and Research (CDER).

2. For inspections of Outsourcing Facilities classified as Official Action Indicated (OAI) due to the failure to comply with section 503B of the Food, Drug, & Cosmetic Act (FD&C Act), section 501(a)(2)(A) of the FD&C Act, or the Current Good Manufacturing Practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act as established in 21 CFR Parts 210 and 211 as they apply to human drugs, OII divisions should, as soon as practical, report significant inspection issues into eNSpect, as per the *Investigations Operations Manual* (IOM), and endorse inspections for advisory, administrative, or judicial actions in accordance with the Regulatory Procedures Manual.

3. The OII Divisions are requested to use this compliance program for all Outsourcing Facility inspections.

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PART I—BACKGROUND

The Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 503B(b),[1] a compounder can elect to register with FDA as an Outsourcing Facility. Drug products compounded in an Outsourcing Facility can qualify for exemptions from the requirements in section 505 of the FD&C Act to have an approved marketing application,[2] the requirement to label drug products with adequate directions for use under section 502(f)(1) of the FD&C Act,[3] and the drug supply chain security requirements in section 582 of the FD&C Act, if the conditions in section 503B are met. Outsourcing Facilities are inspected by FDA according to a risk-based schedule and must comply with other provisions of the FD&C Act, including section 501(a)(2)(A), the CGMP requirements under 501(a)(2)(B), and implementing regulations.

Under section 501(a)(2)(A), a drug is deemed to be adulterated if:

> [I]t has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.

Under section 501(a)(2)(B), a drug is deemed to be adulterated if:

> [T]he methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this [Act] as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

Further, section 501 of the FD&C Act, as amended by the Food and Drug Administration Safety and Innovation Act, states:

> For purposes of paragraph (a)(2)(B), the term "current good manufacturing practice" includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

CGMP regulations for finished drug products, except for PET drug products and medical gas,[4] are established in 21 CFR parts 210 and 211. As stated in the draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020),[5] FDA intends to promulgate more specific CGMP regulations for Outsourcing Facilities. Until these final regulations are promulgated, Outsourcing

[1] 21 U.S.C. 353b.
[2] 21 U.S.C. 355.
[3] 21 U.S.C. 352(f)(1).
[4] The CGMP regulation for medical gas (21 CFR 213) is scheduled for implementation in December 2025.
[5] We update guidances periodically. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Facilities are subject to the CGMP requirements in parts 210 and 211. The primary focus of this compliance program is on those aspects of 21 CFR part 211 that relate to the quality of sterile and non-sterile compounded drugs, including with respect to sterility assurance, strength (e.g., sub-potent, super-potent), labeling, cross-contamination, or drug product mix-ups, because these aspects of Outsourcing Facility operations pose the greatest risk to patient safety if not conducted in conformance with CGMP and other statutory and regulatory requirements.

To facilitate FDA's initiative to enhance the regulation of Outsourcing Facility manufacturing and product quality, FDA may use additional information sources to inform its regulatory oversight. This may include the following: (1) other inspections conducted by FDA; (2) remote regulatory assessments (RRAs)[6], 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.

[6] See Compliance Program 7356.002, Attachment A.

PART II—IMPLEMENTATION

1. Objective

The goal of this compliance program's activities is to ensure that establishments consistently produce 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 conducted 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 establishments[7] are operating in compliance with applicable CGMP requirements to produce sterile and non-sterile compounded drugs. If they are not compliant, provide evidence to act against responsible persons and take appropriate actions to prevent adulterated products from entering the market or to remove adulterated products from the market.

- Provide input to establishments during inspections to improve their compliance with federal regulations.

- Understand current practices in Outsourcing Facilities for the purpose of updating the CGMP requirements, regulatory policy, and guidance documents.

2. Strategy

A. Inspection of Outsourcing Facilities

Drug products are produced using many physical operations that bring together components, containers, and closures to make a product that is released for distribution. Historically, FDA's inspection of drug manufacturing has been organized into sets of operations and related activities called systems. To align with this, FDA's inspections of Outsourcing Facility production activities will also be organized into systems. Control of all systems helps to ensure the firm will produce quality drugs that have the identity, strength, quality, and purity characteristics they purport or are represented to possess.

B. Inspection of Systems

Inspections of Outsourcing Facilities should be conducted and reported using the system definitions and industry codes in this compliance program. Focusing on systems will increase efficiency in conducting inspections because the systems are often applicable to multiple drug products.

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. If a particular system is

[7] In this compliance program, the synonymous terms *establishment*, *person*, *site*, *firm*, and *facility* cover entities subject to FDA regulations and statutory authority for human drugs.

adequate, it should be adequate for all compounded drug products that are produced by the firm. For example, the way an establishment receives, tests, and accepts or rejects raw materials should be the same for all product types. Likewise in the production system, there are general requirements such as the use of SOPs (standard operating procedures), charge-in of components, equipment identification, and in-process sampling and testing which can be evaluated through the selection of multiple products in various production phases. Under each system there may be something unique to a particular process: e.g., the production of Water for Injection, USP (United States Pharmacopeia) for use in producing drug products, the validation of the production process to mill ointments, or performance of dissolution testing. Selecting unique functions within a system for coverage will be at the discretion of the lead investigator.[8]

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. A Scheme of Systems for Production of Drug Products

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 below 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 production of drugs by Outsourcing Facilities consists of the following:

(1) Quality System

This system assures overall compliance with CGMP requirements and internal procedures and specifications. A robust quality system relies on documentation and strong senior management oversight of CGMP operations and quality-related matters, supports and facilitates the activities conducted under the six systems, monitors its effectiveness, and ensures a commitment to an established quality policy.[9] This system includes the quality unit and its review and approval duties (e.g., for quality agreements, change management, risk management, batch release, annual record review, investigations, continued process verification, validation protocols and reports). This system also includes the quality control unit and its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports). It includes all product defect evaluations and evaluation of returned and salvaged drug products. See the CGMP regulations, 21 CFR part 211, subparts B, E, F, G, I, J, and K.

[8] See Part III—INSPECTIONAL.

[9] For purposes of this compliance program, *quality policy* is defined as the overall intentions and direction of an organization related to quality as formally expressed by senior management. See ICH guidance for industry Q10 *Pharmaceutical Quality System*.

(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 the drug products. It includes:

- Building and facility design, material of construction, maintenance, and proper operation.
- Utilities, the output of which are not intended to be incorporated into the product such as heating, ventilation, and air conditioning (HVAC) systems, compressed gases, steam, and water systems (e.g., Water for Injection system).
- Equipment design, material of construction, calibration, and maintenance.
- Equipment qualification (installation and operation qualification). Note that process performance qualification will be evaluated as part of process validation under the Production System.

  Cleaning processes and, where appropriate, cleaning validation.

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, 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 production of 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 production 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 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, 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 inspection option is a surveillance inspection meant to provide a broad and in-depth evaluation of the firm's drug production to assure adequate controls to prevent contamination, collect information about assay and stability testing practices, and evaluate conformance with CGMP requirements. The full inspection option will include an inspection audit of all six systems. A full inspection may be changed to an abbreviated inspection option with OII and OCQC joint concurrence.

(b) Abbreviated Inspection Option

The abbreviated inspection option is a surveillance inspection intended to provide an efficient updated evaluation of conformance with CGMP requirements The abbreviated inspection option may be used if an Outsourcing Facility has a record of satisfactory CGMP compliance with little or no shift in the production operations and with no significant product recall(s), product defect, or significant reported incidents or complaints since the last surveillance inspection. See Part III.1.A (1)(b)- 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 OII and OCQC joint concurrence. The abbreviated inspection option normally will include an inspection audit of at least three of the systems and must include the quality system and the production system. Optional systems are to be rotated in successive abbreviated inspections. During an abbreviated inspection, verification of quality system activities may require limited coverage in other systems.

(c) Selecting Systems for Coverage

The selection of the system(s) for abbreviated inspection option will be made based on the firm's specific operation, history of previous coverage, history of compliance, or other priorities determined with OII and OCQC joint concurrence.

(2) Reinspections

A reinspection is conducted when FDA evaluates inspectional evidence, and determines that the inspection revealed "noncompliance materially related to applicable requirement[s] of [FD&C Act],"

within the meaning of section 744J(4) of the FD&C Act, and FDA has further determined that, based on the inspectional evidence collected, it should conduct the reinspection "specifically to determine whether compliance has been achieved to [its] satisfaction." An inspection assignment memo will be issued for a reinspection and is to be used in conjunction with the compliance program for Outsourcing Facilities.

(3) For Cause Inspections

For-cause inspections are directed inspections performed in response to specific events or information (e.g., receipt of serious adverse event reports, complaints, recalls, and other indicators of defective products) that bring into question the compliance or quality of a manufacturing practice, facility, process, or drug. For-cause inspections provide focused coverage of the areas of concern, the proposed corrective action plan for impacted operations, or any corrective actions implemented to address deficiencies noted on the Form FDA 483, Inspectional Observations from a previous inspection. An inspection assignment memo will be issued for a for-cause inspection and is to be used in conjunction with the compliance program for Outsourcing Facilities. Reinspection fees will be assessed if a for-cause inspection is also a reinspection (i.e., previous inspection was OAI).

(4) State of Control

An Outsourcing Facility is operating in a state of control when it employs conditions and practices that assure compliance with all applicable statutes and regulations, including Sections 503B, 501(a)(2)(A), and 501(a)(2)(B) of the Act. 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.

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 drug products resulting from one or more system(s) cannot be adequately assured. Documented CGMP deficiencies or the failure to meet certain conditions of the FD&C Act 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.

(4) Drug Production

Drug production is a related series of operations which result in the preparation of a drug or drug product. Major operations or steps in a production process may include mixing, encapsulation, tableting, aseptic filling, sterilization, lyophilization, packing, labeling, testing, etc.

(5) Outsourcing Facility Inspection

An Outsourcing Facility inspection is an establishment inspection in which three or more systems, including the Quality and Production Systems, are evaluated to determine if production and compliance with CGMP is occurring in a state of control. The purpose of the inspection is to assess the Outsourcing Facility's conformance with minimum standards for producing compounded sterile and non-sterile drug products, and to prevent the production and distribution of drugs produced under

conditions that may represent a significant risk to patient safety. In addition to coverage of the systems provided for by this program, compliance with certain provisions of section 503B of the FD&C Act may also be evaluated during the inspection.

B. Inspection Planning

After assignment by CDER, OII will prioritize inspections using a risk-based approach. CDER and OII are responsible for determining the depth of coverage given to each establishment. The depth of inspection coverage should be determined by the firm's compliance history, the manufacturing technology employed, the intended patient population, and the characteristics of the products. CGMP inspectional coverage must be sufficient to assess the state of control and compliance for each firm.

When a system is inspected, the inspection of that system may be considered applicable to all products to which it applies. 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 to produce drugs in conformance with CGMP requirements and other applicable statutory and regulatory requirements.

The investigator should select products for which there is the greatest combination of risks to public health. Consider factors such as narrow therapeutic range drug products, processing risks, complaints, volume, distribution, and products with excessive beyond use dates/expiry dates.[10]

[10] See Investigations Operations Manual (IOM), section 5.1.2–Inspectional Approach

PART III—INSPECTIONAL

1. Operations

The investigator should review and use the CGMP regulations for finished pharmaceuticals (21 CFR 210 and 211),[11] sections 503B, 501(a)(2)(A), and 501(a)(2)(B) of the FD&C Act, and the recommendations in related guidance for industry to evaluate manufacturing processes and compliance.

The investigator should conduct inspections according to the STRATEGY section[12] of this compliance program. Recognizing that Outsourcing Facilities vary greatly in size and scope, and production systems are complex, the approach to inspecting each firm should be carefully planned. The complexity and variability of Outsourcing Facilities necessitate a flexible inspection approach that allows the investigator to choose the inspection focus and depth appropriate for a specific facility, but also one that directs the performance and reporting on the inspection within a framework which will provide for a uniform level of assessment. For example, an investigator could conduct a walk-through of the facility and observe production as soon as possible, all while concurrently evaluating the quality system. In some cases, it may be more appropriate for the investigator to review the quality system thoroughly before the walk-through. Furthermore, this inspection approach will provide for fast communication and evaluation of findings.

Inspectional observations noting CGMP deficiencies should be related to a regulatory requirement. CGMP and other requirements for the manufacture of drug products (dosage forms) are in sections 501(a)(2)(A) and 501(a)(2)(B) of the FD&C Act and the regulations in 21 CFR part 210 and 211. CGMP requirements apply to the production of human drugs compounded by Outsourcing Facilities.

Guidance documents are not to be referred to as the basis for an inspectional observation. Observations of noncompliance are based requirements established in the statute and the CGMP regulations. Current Inspection Guides 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 is that the Form 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 Form FDA 483 and in the text of the EIR, referencing the applicability to other systems where appropriate. This approach is used to accommodate the structure of eNSpect, which allows an individual citation only once per Form FDA 483. Refrain from using unsubstantiated conclusions. Do

[11] FDA intends to promulgate more specific CGMP regulations for Outsourcing Facilities. Until these final regulations are promulgated, Outsourcing Facilities are subject to the CGMP requirements in parts 210 and 211.
[12] Refer to section II.2.

not use the term "inadequate" without explaining why and how.[13] Specific specialized inspectional guidance may be provided as attachments to this program, or in requests for inspection.

A. Inspection Approaches

This compliance program provides two surveillance inspection options: full inspection and abbreviated inspection. See the definitions of the inspection options in Part II of this program. A full inspection may change to the abbreviated inspection option with OII and OCQC joint concurrence.

(1) Inspection Options

(a) Full Inspection

The full inspection option includes inspection of all six of the systems listed in Part II of this program. Select the full inspection option if:

- This is an initial FDA inspection of a newly registered Outsourcing Facility. Inspection coverage should include all systems as appropriate to the operations.
- The Outsourcing Facility has a history of fluctuating into and out of compliance. To determine if the firm meets this criterion, OII should utilize all information at its disposal, including compliance history, results of sample analyses, complaints, Drug Quality Reporting System (DQRS) reports, adverse event reports, and recalls.
- Evaluate if important changes have occurred by comparing current operations against operations documented in 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, process, or analytical method requiring new expertise, significant new equipment, or new facilities.
- A full inspection may also be conducted on a surveillance basis at OII's discretion.
- A full inspection may change to the abbreviated inspection option with OII and OCQC joint concurrence and where appropriate.

(b) Abbreviated Inspection

The abbreviated inspection option may be selected with OII and OCQC joint concurrence, and normally will include coverage of at least three systems. Coverage of the quality system and

[13] Refer to policy in the IOM, Chapter 5, Section 5.5.10 – Reports of Observations for further guidance on the content of Inspectional Observations.

production system is mandatory. During an abbreviated inspection, verification of quality system activities may require limited coverage in other systems. This option involves an inspection of the firm to maintain surveillance over the Outsourcing Facility's activities and to provide input to the facility on maintaining and improving the level of assurance of the quality of its compounded drug products. Abbreviated inspection coverage may be changed to the full inspection option with OII and OCQC joint concurrence. Select the abbreviated inspection option if:

- An establishment has a record of sustained acceptable compliance history (e.g., NAI or VAI inspection classifications), a strong risk management program, and a lack of significant marketed product quality defects.

(2) Inspection Coverage

It is not anticipated that full inspections can be conducted every time. To build comprehensive information on the firm's production activities, OII should consider selecting different systems for inspection coverage during successive abbreviated inspections. In addition, coverage can be added on a case-by-case basis by OII prior to or during the inspection in consultation with OCQC. Inspections conducted to follow-up on a warning letter or other significant regulatory actions are considered reinspections, and as a result, the related reinspection may include full systems coverage.

(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 a 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 facility's activities related to producing quality drugs, helps establish and maintain a state of control, promotes robust risk management, and facilitates continual improvement. 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 the guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (October 2006).[14]

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

[14] See also the ICH guidances for industry *Q9(R1) Quality Risk Management* (May 2023) and *Q10 Pharmaceutical Quality System* (April 2009).

requirements and are indicative of an advanced quality system. To aid investigators, Attachment A 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 facility's quality system.

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 production, quality control, and quality assurance and assure 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 which may link to other major systems for inspectional coverage. For sterile compounding operations, this latter objective involves large amounts of data that link to the other inspectional systems. The comprehensive review of such data by the firm is an essential element in assuring that products are produced with a high degree of sterility assurance. It is therefore important to review the firm's system for using the data to assess the state of control of their manufacturing operations and facility. The data summaries and trend reports maintained by the quality unit should be reviewed during every inspection. All data should be attributable, legible, contemporaneous, original, and accurate. During a routine surveillance inspection, this review can help determine which option (Full or Abbreviated) to select.

The firm should have written and approved procedures and documentation that assure product quality. Procedures or documentation may apply to components, containers, closures, in-process materials, compounded drug products, production or analytical equipment, and facilities. 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.

The inspection of the quality system must include a review of all data and reports that may indicate product contamination and sterility assurance issues. For sterile compounded drugs the inspection should also include:

- Quality oversight of contracted operations (e.g., laboratories) and material suppliers to include an: effective monitoring strategy for incoming materials or services, qualification programs, quality agreements, and timely communication channels.

- Management oversight of the development, implementation, monitoring, and continual improvement of the quality system and the incorporation of quality risk management and knowledge management principles.

- Documentation and implementation procedures to ensure hazards (e.g., cross-contamination, adulteration, hazardous impurities such as nitrosamines, 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, completed at least annually, should include information from areas listed below as appropriate:

- Batches reviewed for each product are representative of all batches produced, and trends are identified.

- Evaluations of complaints, adverse events, investigations, retain sample evaluations, rejected lots, stability data, and returned goods that indicate possible product contamination or risks to patients (for example, hazy or cloudy product, foreign matter or particulates in injectable products, cracked or leaky containers).

- Complaint reviews (quality and medical) are documented, evaluated, and investigated in a timely manner. Corrective and preventive actions are implemented when appropriate.

- Discrepancy and failure investigations related to production and testing are documented, evaluated, and investigated in a timely manner using scientific evidence to identify the root cause (or most probable root cause). Corrective and preventive actions (CAPAs) are implemented when appropriate and the effectiveness of the CAPAs is evaluated.

- Discrepancy and failure investigations, such as:

  - All positive sterility tests, and endotoxin and media fill failures regardless of final batch disposition.

  - Unexpected results or trends.

  - All failures that occurred during validation or revalidation of sterilization or depyrogenation processes.

  - All investigations involving media fills (aseptic process simulations).

  - Environmental (microbial/viable and particle/nonviable counts) and personnel monitoring results that exceed alert or action levels.

  - Process deviations or equipment malfunctions that involve critical equipment, such as sterilizers and lyophilizers.

  - Out-of-Specification (OOS) results for assay, impurities, particulate matter, or reconstitution time, if applicable.

  - Product rejects (rejects determined during manufacturing and quality control testing).

- Trends, reports, or summaries of quality indicators:
  - For sterile compounded drugs produced by aseptic processing, a summary of all media fills performed since last inspection.
  - Environmental monitoring trend data (microbial and particle counts)
  - Personnel monitoring trend data
  - Summary of water system test results

- Documentation of change management, including justification for changes, for the manufacturing of all products. Quality risk management principles are used to evaluate proposed changes for potential risks (e.g., hazardous drugs and microbial contamination) and impact on product quality. Proposed changes should be reviewed by subject matter experts and approved before implementation and any necessary (re)evaluation, or (re)qualification should be completed. Changes should be evaluated for effectiveness.

- Summary of change controls for critical utilities and equipment implemented since the last inspection, for example:
  - Sterilizers, lyophilizers and depyrogenation equipment
  - Aseptic processing line(s) (e.g., automated filling equipment, ISO 5 laminar air flow hoods)
  - Clean steam generator, process gas system
  - Water for Injection (WFI) system and Purified Water system
  - Air handling systems
  - Automated building management system

- Investigation of rejects, and the investigation should be expanded when warranted. CAPAs should be implemented when appropriate.

- Investigation of stability failures, and the investigation should be expanded when warranted. The need for recalls should be evaluated and impacted products should be appropriately dispositioned.

- Quarantine products.

- Validation: Approval of required validation or revalidation (e.g., computer, production process, laboratory methods) is documented.

- Training and 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. Significant issues are escalated to senior management.

- Assessment of returns/salvaged products are assessed; investigations are expanded when warranted, and these products are appropriately dispositioned.

In addition, the review of summary data and observation of operations can focus the inspection on potential problem areas and provide an overview of the effectiveness of the quality system. The inspection of the quality system may necessitate follow-up coverage within another system. However, this coverage may not constitute or require complete coverage of these systems.

(b) Facilities and Equipment System

The principal objective of an effective Outsourcing Facility operation from a facility and equipment standpoint is to provide suitable protection of compounded drug products. The inspectional evaluation of this objective is also two-phased:

- Review and evaluate the firm's rationale for, and adequacy of, the facility and equipment design.

- Evaluate the data that provides information relevant to the state of control of the facility and equipment.

The firm should have written and approved procedures and documentation for process equipment, the design of the facilities (e.g., unidirectional vs. two-way personnel, materials, equipment, and product flows, designated vs shared areas) and utility systems that support the critical physical and chemical requirements of compounded drug products (e.g., design and construction, installation qualification, operation qualification, calibration, and maintenance, controls, and automation). 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, all areas listed below should be covered. However, the depth of coverage may vary depending upon inspectional findings.

In addition to the review of design elements and data, investigators should look for visible deficiencies in the facility and equipment, such as uncleanliness, equipment deterioration (e.g., warping, corrosion, staining), inaccessible or difficult to clean surfaces, and changes to critical equipment or systems that have not been qualified and which may impact product quality. Investigators should look for aberrant events due to facility deterioration, a pattern of recurring and uncorrected maintenance issues, and an increase or changes in production output that exceed the capacity of the facility and equipment.

i. Facilities

The inspectional evaluation should:

- Evaluate the design and layout of the facility (e.g., personnel and material flow, cleanroom design and material of construction, air filtration and exhaust) for the prevention of cross-

contamination[15] (e.g., HVAC system designed to prevent the influx of poor-quality air or penicillins, non-penicillin beta-lactams, steroids, hormones, or cytotoxic or highly sensitizing drugs).

- Review the certification and qualification of the clean room areas to verify these areas meet the established design criteria and specifications. Certification and qualification typically include data in support of the following: airflow pattern studies (unidirectional airflow where applicable), HEPA (High Efficiency Particulate Air) filter integrity testing, air velocity measurements, nonviable particle counts, and verification of appropriate pressure differentials, temperature, and humidity setpoints.

- Assess if specifications for clean room areas (e.g., air classification, pressure differentials between rooms and areas, temperature, and humidity) are appropriate, and based on the risk of product contamination with particulate matter and microorganisms.

  – Evaluate the airflow pattern studies (smoke studies) conducted under dynamic conditions to verify the unidirectional airflow and any air turbulence observed within the critical area where sterilized drug product, containers, and closures are exposed to environmental conditions. If possible, review video recordings for airflow pattern studies (smoke studies).

- Ensure routine monitoring and maintenance to assure air handling systems continue to operate within established parameters (microbiological monitoring is discussed under the Laboratory Control System):

  – Afford special attention to facilities that are performing construction in the clean areas, or at the vicinity of a cleanroom. Because microbes (e.g., fungal spores) can be liberated from the movement of walls and other construction activities, determine if the facility is returned to acceptable environmental control through proper measures (e.g., environmental monitoring, media fills) before production is allowed to resume.

  – Verify that environmental monitoring of viable and nonviable particles is occurring during operations including locations where there is the most risk to exposed product, container, and closures.

  – Check if pressure differentials, temperature, and humidity are monitored during routine production.

  – Determine if monitoring systems have alarms to alert operators of excursions.

  – Check if excursions from acceptable ranges are investigated to determine impact on product and that needed corrective actions are taken.

[15] See the draft guidance for industry *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination* (June 2022). When final, this guidance will represent the FDA's current thinking on this topic.

- Check if critical equipment (e.g., laminar airflow hoods, restricted access barrier systems, isolators, etc.) that has been moved is requalified before use.

- Evaluate cleaning and maintenance.

  - Review sanitation of the building, use of appropriate rodenticides, fungicides, insecticides, cleaning, and sanitizing agents. Controls are established to prevent contamination, particularly with any pesticides or any other toxic materials, or other drug or non-drug chemicals.

  - For multiuse facilities and non-dedicated equipment, evaluate the adequacy of the changeover procedures and cleaning to prevent cross-contamination between products.

  - Sanitization or disinfection of clean room areas, processing lines, and non-autoclavable equipment, materials, and components should be reviewed to ensure they are suitable for their intended use (e.g., non-sterile disinfectants or shedding wipes would not be appropriate to sanitize or disinfect cleanrooms). Investigators should focus on the areas where the sterile product is exposed up to and including sealing operations. These critical areas represent the highest risk to products that are intended to be sterile. The suitability, efficacy, and limitations of disinfecting agents and adequacy of cleaning procedures should be reviewed, including the data that establishes the expiry of the disinfection solution. Note: published literature and supplier certificates of analysis can be relied on when initially determining the effectiveness of agents used to clean and disinfect, as necessary, the facility and equipment surfaces, provided that the supplier's cleaning procedures are followed. Examples of insanitary conditions[16] include but are not limited to:

    - Visible signs of filth, dirt, dust, mold or mildew, insects, inappropriate items/debris, trash, or other signs of inadequate cleanliness on floors, ledges, and other surfaces

    - In processing areas: peeling paint, chipped drywall, or ceiling tiles in disrepair, perforated, unsealed or difficult to clean.

  - Control system for implementing changes in the building.

  - Lighting, potable water, washing and toilet facilities, sewage and refuse disposal.

  - Oversight of facility infrastructure and suitability of manufacturing operations by responsible operations manager.

[16] See the guidance for industry *Insanitary Conditions at Compounding Facilities* (November 2020).

ii. Equipment

The investigators should evaluate:

- Equipment installation qualification, operational qualification, performance qualification, calibration, and maintenance where appropriate (e.g., smoke studies or airflow visualization for ISO 5 environments, HEPA certification).
- Adequacy of equipment design, size, and location (e.g., equipment for ISO areas, cleanroom activities, and cleanability).
- Equipment surfaces to determine whether they are reactive, additive, or absorptive.
- Product risk from equipment within production areas (e.g., equipment stored or operated in ISO 5 areas that could compromise the air quality).
- Appropriate use of equipment, lubricants, coolants, refrigerants, etc. that may contact products, containers, or closures.
- Qualification, calibration, and maintenance of storage equipment (e.g., refrigerators, freezers) to ensure that reference standards, raw materials, reagents, or other materials are stored at the proper temperature.
- Equipment qualification, calibration, and maintenance (e.g., autoclave, incubators, and water baths qualification and maintenance records), including computer qualification and computer system validation.
- Sterilizing filters are appropriately sourced and checked for integrity post-use.
- Equipment identification practices (where appropriate).
- Documented investigation into any unexpected discrepancy.
- Control system for implementing changes to equipment.

Equipment used in the manufacture of sterile drug products may include, but not limited to, the following: 1) production equipment, 2) container/closure processing equipment (e.g., stopper washer, glassware depyrogenation equipment), 3) support system/material system related equipment (e.g., WFI system and related equipment, process gas related equipment).

(1) Production Equipment

a. **Aseptic Processing Equipment.** Determine that all equipment that comes in direct contact with product (e.g., filters, transfer lines, holding tanks, stopper bowls,

filling line equipment) and sterile components (e.g., stoppers) are sterilized and protected from contamination prior to and during use. Equipment logs or other related information may provide insight into significant maintenance or other problems that may increase exposure of batches to contamination risk.

b. **Stopper Washer.** Inspectional considerations include the qualification of the equipment, cycle validation and supporting data, equipment preventive maintenance (maintenance requirements and frequency), quality of water used for washing, and associated water sampling/qualification data. The appropriateness of the air supply used in any drying operations should also be verified.

c. **Capping Equipment (Vials).** The vial cap provides the final closure element of a sealed vial. The capping machine folds and crimps the cap (aluminum) over the neck of the stoppered vial. The cap on the vial protects the stopper from external damage, while firmly holding the stopper in the fully seated, sealed position. Evaluate the established processing settings (crimp angles, pressures), and preventive maintenance schedules of the capping machine. Air supply quality to the capping units should also be evaluated. Ensure that containers are fully sealed/capped before exposing to less than ISO 5 quality air.

d. **Post-Fill Visual Inspection / Automated Inspection Equipment.** The 100% inspection of the final filled and sealed product may occur via a manual, automated, or semi-automated inspection process. Manual and semi-automated inspection processes involve specified viewing fields and calibrated light sources. Semi-automated processes may use conveyor belts and rotational units that present the filled product to an operator for visual inspection. All conveyor and rotational speed set points should be verified against established parameters. Automated inspection systems may inspect for one or more types of defects in each filled product. Defect categories with relevant action levels should be defined. The qualification of the equipment and the challenges performed to verify equipment functionality prior to routine use should be evaluated as well as the training program for operators performing manual visual inspections.[17]

e. **Sterilizers.** The inspection should cover the Installation and Operation Qualification of equipment, the performance qualification of the process (Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ)), and operation, calibration, and preventive maintenance of representative types of equipment used to sterilize finished dosage forms, filling equipment, containers, closures, etc. Such equipment includes autoclaves, dry heat ovens, dry heat tunnels, steam-in-place equipment, and chemical sterilization systems (i.e., hydrogen peroxide, peracetic acid). Inspection of sterilizers should

[17] See the draft guidance for industry *Inspection of Injectable Products for Visible Particulates* (December 2021). When final, this guidance will represent the FDA's current thinking on this topic.

include physical examination of the equipment. Review the engineering specifications, which may be described in the equipment's DQ (Design Qualification). DQ is performed prior to the IQ and OQ. Verify that the sterilizer is maintained, calibrated, and drained properly and that it has appropriate measuring devices (temperature sensors, pressure gauges, etc.).[18]

i. Records of unplanned maintenance, as well as preventive maintenance, should be reviewed to assure all significant changes have been evaluated and qualified as appropriate. Equipment logs should also be reviewed. For example, repeat sterilization of loads because of cycle failures can indicate a serious problem with a sterilizer. Impact of re-sterilization to product quality should be evaluated. (PQ is covered under the production system).

ii. The equipment can be computer-controlled or operated in a manual mode. For computer-controlled systems, programmable logic controller or a more complex Supervisory Controlled and Data Acquisition Management System (SCADA) may require an assessment to determine if the computer control and/or monitoring system are Part 11 compliant.

f. **Lyophilizer.** Because partially sealed vials are used in the lyophilization process, sterile product is exposed to the environment from the time of filling until the vials are fully stoppered in the lyophilization chamber at the end of the cycle. The inspection should verify that partially sealed vials are transported and loaded into the lyophilizers under Class 100 (ISO 5) protection. Investigators should observe the transport of vials and loading of lyophilizers. Other key equipment areas to cover include validation of the sterilization of the lyophilization chamber between uses, current sterilization controls, leak testing of the chamber, integrity testing of air/gas filters, and calibration of temperature and pressure controllers. Reference: FDA's Guide to Inspections of Lyophilization of Parenterals.

g. **Isolator.** Evaluate the design and control elements that maintain the separation or isolation of the product. Pressure differential, glove integrity, and protection of the transfer (i.e., entry, exit) ports are key elements for the isolators. The transfer of containers, closures, and supplies (including environmental monitoring supplies) into an isolator should be carefully controlled. Another critical element for these systems is the effectiveness of the chamber decontamination program. Current methods (e.g., vaporized hydrogen peroxide, steam hydrogen peroxide, peracetic acid) used to decontaminate isolator barriers are capable of surface sterilization but lack the penetrating capabilities of steam sterilization. Investigators should be mindful of the limitations of these surface sterilants, including their inefficiency in penetrating obstructed or protected surfaces. Validation of the decontamination of the interior (surfaces) of an isolator should demonstrate a 6-log reduction of the biological indicator (BI). Quantitative measuring devices (e.g., near infrared) or

[18] See PDA Technical Report No. 1 (Revised 2007) Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control; and ISO 17665 Moist Heat Sterilization.

chemical indicators (qualitative test) can be used to determine the worst-case location for decontamination validation using a BI. Factors to be considered in decontamination validation include the location of the BI and the type of surfaces where the BIs are inoculated.

i. Utensils and equipment surfaces inside the isolator that have direct contact with sterile product and components should be sterilized to render them free of microorganisms. The sterilization validation should achieve a minimum of a 6-log reduction of the BI.[19]

h. **Restricted Access Barrier System (RABS).** [20] In general, a RABS is a fill-finish line in a rigid wall enclosure that provides full physical separation of the filling line from operators. It is important to note that the inside surfaces of the RABS are disinfected with a sporicidal agent, but this is not accomplished using the automated decontamination cycles employed for isolators. This requires firms to carefully supervise disinfection procedures and assure ongoing effectiveness of the disinfection program. Operators use glove ports, half suits or automation to access areas within the enclosure during filling. There are two types of RABS, "open" and "closed" RABS. The doors to a "closed" RABS are never opened during an operation. While an "open" RABS is designed to operate with doors always closed, on rare pre-defined circumstances the doors of the enclosure can be opened to perform certain interventions. If doors are routinely opened during a filling operation, the system is not considered a RABS because it no longer restricts access to the critical areas. Typically, the cleanroom surrounding the RABS is controlled as a Class 10,000 (ISO 7) area and operators are fully gowned. When inspecting a RABS:

i. Determine that the gloves and gauntlets attached to the glove ports are sterile when installed. After installation, the gloves should be disinfected or changed at appropriate intervals to minimize the risk of contamination.

ii. Verify there is a well-defined written procedure that describes what is done when an open-door intervention is performed. All open-door interventions should be documented and described in batch records, and followed by disinfection.

iii. RABS entry is often accompanied by an appropriate line clearance, which should be clearly documented in batch records.

iv. Determine that all fluid pathways and product contact parts such as stopper bowl, feed and placement systems are sterilized prior to the filling of each

[19] See PDA Technical Report 51 (2010), Biological Indicators for Gas and Vapor Phase Decontamination Processes: Specifications, Manufacture, Control and Use. This document provides general principles to be considered in decontamination by BI.
[20] See Restricted Access Barrier Systems (RABS) for Aseptic Processing, ISPE (August 2005).

batch.

v. Observe how sterile components and supplies are transferred to the RABS. Verify that the transfer system prevents exposure of sterile surfaces to less clean environments.

vi. Verify that non-product contact surfaces within the RABS undergo thorough disinfection with a sporicidal agent before each batch. The effectiveness of the overall disinfection program should be validated and routinely evaluated by the environmental monitoring program.

i. Laminar Flow Hoods (LFHs). LFHs must provide ISO 5 or better conditions and unidirectional airflow must be ensured to reduce the risk of product contamination. Inspectional considerations include review of: IQ, OQ, PQ, and validation of the LFH; evaluation for continuous monitoring of nonviable particle counts and air quality; regular maintenance, including a routine preventative maintenance program and evaluation of the HEPA filter(s); and environmental monitoring for viable and nonviable particles. Airflow patterns should be performed under dynamic conditions and evaluated for turbulence or eddy currents that can act as a channel or reservoir for air contaminants.

j. **Blow-Fill-Seal (BFS) Technology.** BFS is an automated aseptic filling process in which containers are formed, filled, and sealed in a continuous operation. BFS systems can reduce the risk of product contamination by reducing operator interventions. The systems are typically used for filling sterile ophthalmic and respiratory care products.[21] It should be noted that the inner surfaces of the containers can be exposed to the surrounding environment during the formation and molding steps prior to filling. The sterile product can also be exposed to the environment during the filling and sealing steps of the BFS process. Therefore, the air quality should meet the microbiological level established for Class 100 (ISO 5) and should be supplied to where the sterile product or its containers are exposed during the BFS process. Some of the more advanced BFS equipment that provide enhanced protection for the sterile product operation can be in a Class 100,000 (ISO 8) area. Otherwise, a Class 10,000 (ISO 7) area is appropriate. Research has demonstrated a direct relationship between the number of contaminated units and the level of microbial contamination in the air surrounding the machine.[22] Typically, the product supply line and sterilizing product filters are steam sterilized in place. When inspecting BFS:

i. Verify that HEPA-filtered or sterile air is used during steps where sterile product or materials are exposed (e.g., parison formation, container molding, and filling steps).

[21] See Appendix 2 of the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process* (October 2004).
[22] ISO 14698 Cleanrooms and Associated Controlled Environments Biocontamination Control.

ii. Routinely evaluate the monitoring and preventive maintenance programs to determine the integrity of the utilities (cooling water, heating, etc.) associated with the BFS. Leaks in the molds or utility connections at the molds can contaminate the sterile product or containers.

iii. Review the sterilize in place (SIP) system used to sterilize the product line. Determine the sterilization cycle has been validated and the condensate properly drains from the line. The line should also be protected between sterilization and use.

iv. Verify that personnel who enter the classified environment surrounding the BFS machine are properly gowned and trained.

v. If possible, observe equipment setup and any difficulties that can lead to contamination risks.

vi. Other control procedures (media fills, environmental monitoring, disinfection of surfaces, etc.) should be the same as discussed for a conventional aseptic processing line.

(2) Container/Closure Processing Equipment

Depyrogenation equipment may include a dry heat oven and/or depyrogenation tunnel. Depyrogenation of stoppers can also be accomplished by dilution via a washing process. The final rinse of the washing process uses WFI. Evaluate depyrogenation processes to ensure they are appropriately validated for destroying or removing pyrogens (e.g., endotoxins).[23]

(3) Support System Equipment

a. **Water System**. Specifically, review WFI generation equipment and distribution loop(s), including tanks, water lines, isometric diagrams, vent filters, and preventive maintenance schedules (See also Materials System). Monitoring equipment associated with the Water System should also be evaluated.

b. **HVAC**. Refer to Section IV of the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process* (October 2004), specifically the part on qualification and maintenance of the HVAC system.

c. **Process Gases**. Gases that are in contact with the drug product or components in drug manufacturing operations are referred to as process gases. Gases used in aseptic operations, or downstream of sterilization, must be filtered through a sterilizing grade filter to maintain asepsis. The integrity testing of these filters

[23] See the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process* (October 2004).

(typically hydrophobic) should be evaluated. The system used in the generation of the process gas(es) should also be evaluated including preventive maintenance schedules, monitoring (including temperature, pressure, and humidity), and sampling. See also under Materials System.

(c) Materials System

The principal objective of an effective Outsourcing Facility operation from a materials standpoint is to provide suitable components, containers, and closures. In sterile operations, the quality attributes of each of the materials (ingredients, WFI, containers, closures) have a bearing on the critical attributes of the finished product. Each Outsourcing Facility is expected to implement procedures and controls for the components, containers, and closures to ensure compounded drug products meet all established quality specifications over the expiry period.

The suitability of containers and closures should be evaluated by the Outsourcing Facility using scientifically sound and appropriate criteria to verify suitability and conformance to all relevant quality specifications. The integrity of the container/closure system is critical to assuring that all units of drug products remain sterile through shipment, storage, and use. Leaking containers or closures lead to product contamination. Evaluate the firm's efforts to ensure containers and closures protect the product throughout the marketed shelf life and are also not reactive, additive, or absorptive. Review the firm's procedures and practices for handling and storing container/closures to protect them from deterioration or contamination. Evaluate the firm's adherence to the supplier's expiration date or in-use/retest date. Assess if containers/closures are re-examined/retested after stored for long periods or exposed conditions that may adversely affect the container/closure. Evaluate the firm's procedures for cleaning and where applicable sterilizing and depyrogenating container/closures.

Appropriate controls are expected for all components (sterile and non-sterile) to ensure the quality of the finished compounded drugs. Scientifically sound and appropriate specifications must be established for each component to address all necessary quality attributes of the finished drug product given the intended use, route of administration, and any other conditions specified in the drug product directions for use.

In general, component quality attributes may include but are not limited to identity, strength, purity, particle size, sterility, bacterial endotoxin level, content uniformity, sterility (or for non-sterile products, microbial enumeration, tests for specified microorganisms) and other characteristics (e.g., product-specific tests established by official compendium) that could affect the quality of the final drug product. Review the firm's established specifications for components as well as the firm's scientific basis for establishing specifications for each component. Evaluate the firm's controls for examining, testing, and accepting components.

Determine if the firm tests, examines, or verifies the acceptability of each lot of components, and each shipment if shipped separately, and if conformity with all specifications is evaluated before use. Evaluate the firm's procedures and practices for storing components (e.g., stored under the supplier's labeled storage conditions or otherwise established using scientifically sound and appropriate criteria). Assess if components are used within expiry or retested and re-examined, where appropriate. In the absence of supplier's labeled expiration (or retest) date, review the firm's internal

controls for setting expiration (or retest) date, or use by dates.

When this system is selected for coverage, all areas[24] listed below should be evaluated:

- Qualification of suppliers and vendors.
- Identification, including labeling, of components, containers, closures.
- Examination, including package integrity, of components, containers, closures.
- Storage conditions of components, containers, closures.
- Storage under quarantine until tested or examined and released.
- Representative samples collected, tested, or examined using appropriate means for each lot.
- Each lot of containers and closures is examined to ensure conformity with appropriate specifications before use or in lieu of, verification of the supplier's test results (certificate of analysis or conformity) for components, containers, and closures.
- Evaluate the tests and studies performed to demonstrate the integrity of container closure systems for all sterile drugs, including confirming that container closure integrity is demonstrated during validation and as part of the stability program (in lieu of sterility testing), over the shelf life of the product.
- Where applicable, conformance to compendial standards (i.e., applicable USP/NF general chapters and monographs).
- For sterile drug products: a validated sterilization and depyrogenation process for container/closures (if not using presterilized, and depyrogenated containers and closures); and where applicable, validated washing prior to sterilization in-house.
- Water produced onsite and used as an ingredient or processing aid tested for appropriate quality given the intended use to include:
  - Design and qualification of the water generation and distribution system
  - Offline and in-line monitoring (e.g., pH, TOC, conductivity), trending of data
  - Sampling sites, procedures, microbial alert, and action levels
  - Preventive maintenance, periodic cleaning, and calibration
  - Investigations for discrepancies and excursions

[24] For each of the listed areas, the firm should have written and approved procedures and/or documentation resulting therefrom. These areas are not limited to finished products but may also incorporate in-process materials. The firm's adherence to written procedures should be verified through observation whenever possible. However, the depth of coverage may vary depending upon inspectional findings.

- Process gas supply, design, maintenance, validation, and operation.
- Appropriate handling and protection of sterile containers and closures (i.e., packaging integrity maintained during storage or movement in non-aseptic environments).
- Rejection of any component, container, closure not meeting acceptance requirements including any supplier established expiration or in-use period.
- Appropriate retesting/reexamination of components, containers, closures.
- First in – first out use of components, containers, closures.
- Where necessary, retesting and reexamination of components for identity, strength, quality, and purity.
- Quarantine of rejected materials.
- Documented investigation into any unexpected discrepancy.

(d) Production System

The principal objective of an effective production system is to ensure process controls are designed and followed to ensure the drug products manufactured have the identity, strength, quality, and purity they purport or are represented to possess. Each Outsourcing Facility is expected to have written and approved procedures, documentation, and controls. 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. The inspectional evaluation for this objective includes:

- Review and evaluate the firm's personnel, material, equipment, product, and process flow.
- Evaluate the data that provides information relevant to the state of control of the Outsourcing Facility's manufacturing operations.

Production practices and conditions can have a direct and significant adverse impact on drug sterility assurance. Coverage of critical elements of the production system, which are typically defined by the firm, should be part of all inspections of Outsourcing Facilities.

The risk of contamination posed by an operation depends greatly on the design of the overall manufacturing operation. Observation of manufacturing is a critical part of evaluating the adequacy of an aseptic processing operation. Before use in production, equipment, components, containers, and closures should be visually examined for indications of damage, degradation, or contamination. All aseptic manipulations, including processing of sterile materials, filling, and closing (e.g., placement

and sealing of stoppers on vials), should be performed under unidirectional flow that is ISO 5 or better.[25]

The following should be carefully reviewed and observed:

- Adequacy of personnel practices, aseptic technique, and adherence to documented procedures.
- Movement of people and materials before and during the aseptic operation.
- Robustness of production process design (e.g., process performance, validation, impact of equipment configuration on ergonomics of aseptic manipulations).
- Established justifiable time limits for completion of phases of production including in-process storage conditions and hold times (e.g., bulk in-process time/temperature, partially stoppered vials during loading/unloading for lyophilization).
- Process validation, including validation and security of computerized or automated processes.
- Identification of equipment with contents, and where appropriate, phase of manufacturing and/or status.
- Adequate procedure and practice for charge-in of components (e.g., sterile operations outside ISO 5).
- Method of sealing containers with closures (e.g., manual or automated stoppering, and use and application of caps and crimp seals).
- Disinfection practices, including suitability and efficacy assessment of cleaning/disinfection practices, and verification of stated product label process.
- Validation of cleaning/sterilization/depyrogenation of components including equipment, containers, and closures (e.g., validated for bioburden reduction).
- Equipment cleaning and use logs.
- Contamination and cross-contamination controls.
- Prevention of objectionable microorganisms in non-sterile drug products.

[25] See the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process* (October 2004) and draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). When final, this guidance will represent FDA's current thinking on this topic. See also Compliance Program 7356.002, Drug Manufacturing Inspections.

- Contemporaneous and complete batch production documentation (batch production and control records; master production and control records).
- Calculation and documentation of actual and percentage of theoretical yields.
- Formulation at not less than 100%.
- Control system for implementing changes in processes.
- Implementation and documentation of in-process controls, tests, and examinations (e.g., Visual Inspection, pH, adequacy of mix, weight variation, clarity).
- Justification and consistency of in-process specifications and drug product final specifications.
- Change control; the need for revalidation evaluated.
- Documented investigation into any unexpected discrepancy.
- Sterilization method and validation.
- Defects in container/closures after production.

More specifically, the inspection should include real time observation of the higher risk operations including but not limited to (these are examples and not an all-inclusive list):

- Adherence to production procedures (e.g., setup, line clearance, aseptic processing, environmental and personnel monitoring)
    - Setup of filling lines, especially difficult to assemble lines (e.g., powder filling lines), and lines that require multiple aseptic assemblies or do not employ SIP of the product pathway.
- Cleaning and disinfection of the line and room to ensure all difficult-to-access surfaces are consistently and properly cleaned and disinfected.
- Protection of critical contact surfaces to ensure their sterility throughout operations and post sterilization (exceptions may be considered for products undergoing terminal sterilization).
    - If a drug product intended to be sterile is not terminally sterilized, there must be a validated sterilization step such as sterile filtration and it is critical that the sterilization step occur as close to filling into the final product container as is feasible.
- Aseptic technique and cleanroom behavior during operations, including handling of equipment jams and stoppages.

- Personnel flow in relation to microbial control of the environment.

- Material flow (e.g., whether materials are moved from a lesser controlled area to a cleaner area without disinfection), including number of staff and their activities in the aseptic filling room.

- Filling operations, especially personnel gowning technique, gown integrity, strict adherence to SOPs, the nature and frequency of interventions (interventions should also be performed during the media fill simulations), and overall condition of the critical filling area.

- Atypical interventions associated with unplanned events (e.g., operator attempts to change the filling pump during operations).

- Extra manipulations during filling operations for assembly of sterile filtration apparatus that is not sterilized in place.

- Handling (transfer, storage, loading) of partially stoppered vials in lyophilization processes. Note that for lyophilized products, vials of sterile products are stoppered but not fully sealed until the lyophilization process is completed. The sterile product is exposed to the environment during filling, half-stoppering, transport, loading of the lyophilizer, and the lyophilization cycle. Complete seating of stoppers typically occurs in the chamber after the cycle is completed. These manipulations must be performed under ISO 5 conditions.

- Preparation of equipment for sterilization (cleaning, use of the type of wrapping to ensure protection while still allowing for penetration as part of the validated sterilization cycle with defined loading patterns).

- Environmental monitoring (while the monitoring program is considered a Laboratory System, inspection should include observation of the actual monitoring operations and rationale for sample site locations).

- Proper placement and sealing of stoppers on vials as applicable; capping (aluminum crimp) is performed in a classified area under unidirectional flow in ISO 5 or better conditions.

- Production of sterile suspensions and sterile bulk powders (e.g., antibiotics) where sterile filtration of the final bulk is not feasible. These are typically formulated and manufactured under aseptic conditions. This requires the sterilization of large pieces of production equipment (e.g., tanks, reactors, dryers, and associated lines) and assurance that these pieces of equipment retain their integrity and remain sterile.

Critical operations that should be covered during an inspection of the production system include:

i. Media Fills or Process Simulations

Media fills are used to validate aseptic processing operations, including those employing newer technologies, such as isolators, BFS or RABS systems. Media fills representing manually intensive aseptic operations should equal or approach the size and duration of a commercial production lot. In contrast, a process conducted in an isolator is designed to have a lower risk of microbial contamination because of the lack of direct human intervention; therefore, it can be simulated with a lower number of units as a proportion of the overall operation. All media fills should closely simulate manufacturing operations, incorporating, as appropriate, worst-case activities and conditions as well as operator interventions.[26] The media fill program should address:

- Factors associated with the longest permitted run of the aseptic processing operation that can pose contamination risk (e.g., operator fatigue, quality of processing environment).

- If the firm prepares its own media, determine if the firm prepares the media correctly, tests the pH, and conducts a growth promotion test.

- Representative number, type, and complexity of normal interventions that occur with each run, as well as nonroutine interventions and events (e.g., maintenance, stoppages, equipment adjustments). The maximum number of expected interventions should be included to simulate worst-case conditions.

Inspection actions should include:

- Review to ensure the media is within expiry at the time of use.

- Verify media fills represent actual manufacturing operations by comparing observed operations to those documented in Media Fill batch records.

- Determine if the firm conducts media fills or process simulations under the most stressful/challenging conditions (including simulations of environmental and personnel monitoring).

- Review if aseptic operators are initially qualified and requalified thereafter.

- Determine if media fills are conducted semi-annually for each processing line or when process changes occur. The activities and interventions representative of each shift should be included in the semiannual media fill program. This may require more than one media fill per line every 6 months if aseptic processing is performed during more than one shift. Except for isolator operations, at least one semiannual media fill should be performed per line per shift. Determine if the aseptic filling of all types of containers is supported by the media fills performed. If a matrix approach is used, evaluate the firm's justification for selecting the worst-case container/closure configurations for each line.

[26] FDA's current expectations for media fills are discussed in Section IX.A of the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process* (October 2004).

- Determine accountability of all filled units (units filled vs. units incubated).
- Determine if the firm takes appropriate actions for a failed media fill.
- Verify that all units that were discarded during and after filling have a reasonable and assignable cause for rejection (e.g., rubber stopper missing, aluminum cap missing). All integral units should be incubated.
- Determine that any cracked and leaking units found after incubation are investigated, counted and all rejected units properly justified (e.g., is there an assignable cause that is reasonable for the rejection?).
- Determine how and who examines units after incubation. If the examination is not performed by a microbiologist, determine if it is overseen by the quality unit and if the operators doing the exam are properly trained by qualified personnel.

ii. Sterile Filtration (Aseptic Processing)

If a drug product intended to be sterile is not terminally sterilized, the finished drug product should be sterilized immediately before filling into the final product container. This is typically done by filtration; however, other validated sterilization methods may be used. If a finished drug product cannot be filtered (e.g., certain suspensions), components should be sterilized (e.g., by filter) at the last possible step (e.g., before forming the suspension). Manipulations following the component sterilization step must be designed to prevent microbial contamination of the drug product.

Inspection actions should include:

- Verify filters used in production are identical to those used in validation studies.
- Verify that actual operating parameters and allowable extremes (e.g., batch filtration volumes, flow rate) are covered in the validation studies.
- Determine that validation of filter sterilization has been performed for all products.
- Observe filter integrity testing to verify procedures are followed.
- Review investigations of any integrity test failures.

iii. Sterilization and Depyrogenation of Containers, Closures, and Processing Equipment

Review the validation or revalidation of sterilization and depyrogenation processes used for containers, closures and, in the case of aseptic processing, equipment that contacts the sterile product or sterile components. Check if the firm verifies that validated parameters (loading patterns, cycle

parameters) are met for each load. Rubber stoppers that are not purchased pre-sterilized or pre-siliconized may require depyrogenation and siliconization prior to use. As previously noted, depyrogenation may be achieved via a washing process with the use of repeated WFI washing steps. The validation should demonstrate a successful 3-log reduction of bacterial endotoxin. When the firm performs its own siliconization of stoppers, silicon level after wash should be validated to meet the predetermined acceptance criteria. For stoppers that are sterilized by steam sterilization, verify that the clean steam used to provide the sterilization is acceptable and has been assayed for endotoxin.

Inspection actions should include:

- Review the practices and procedures to determine if the firm needs to revalidate the sterilization and depyrogenation process.
- Review change control procedures.
- Determine if reprocessing is performed.
- Evaluate bioburden level: Evaluate the firm's understanding of process bioburden (e.g., from incoming components/container/closure) and determine if the firm has adequately validated hold time for critical steps.[27]

The microbiological content (bioburden) of articles and components that are subsequently sterilized should be controlled. If materials are stored or held during processing (e.g., before sterilization, after sterilization, before container fill), storage or holding times must be established. Production phase hold times for a drug product should be limited, verified by testing, and based on an understanding of the associated risk of increased bioburden and endotoxin. Hold time assessments can be performed as part of the process for validating sterility assurance. In addition, in-process materials such as bulk stock solutions must be stored in equipment that is protective and does not affect the quality of the drug beyond its established specifications.

iv. Lyophilization

Inspection actions should include:

- Review the validation of lyophilization cycles established for selected products.
- Verify the firm confirms all critical cycle parameters are met for each lot.
- Determine environmental monitoring is routinely (at least daily) performed in the areas of loading and unloading of the product from the lyophilizer. In addition, ensure personnel

[27] It is important to note that increased bioburden can lead to sterilization/endotoxin failures as well as the degradation of the drug product, contributing impurities to the drug product. Sampling points (location in process flow) and methods should be evaluated based on product quality risks.

monitoring is conducted on those operators who perform the loading and unloading operations.

- Observe the transport of the partially stoppered vials and the loading of the lyophilization chambers to verify these steps are done under proper environmental conditions (ISO 5) and to verify that proper aseptic techniques are used.

v. Sealing of Vials

A vial is not completely sealed until the aluminum overseal is placed over the rubber stopper and crimped in place. If stoppered vials exit the aseptic processing zone prior to capping, verify proper safeguards are in place, such as HEPA-filtered air protection and qualified in-line detectors that reject vials with improperly seated stoppers.

vi. Terminal Sterilization

For sterile drug products that are terminally sterilized, at least a 10^{-6} sterility assurance level should be demonstrated in validation studies during process development using an appropriate sterilization load monitor, such as biological indicators and thermocouples. Validation studies should be performed for each load size (container closure and number of vials) intended for sterilization. For terminally sterilized drug products that are not subjected to an overkill terminal sterilization cycle, pre-sterilization bioburden limits should be established (i.e., determining the number of microorganisms that can be reliably killed) and measured before sterilization. Terminal sterilization methods may include dry or moist heat, ionizing radiation, ethylene oxide (EtO) gas, or vaporized hydrogen peroxide. The selected sterilization method should both sterilize and not have a deleterious effect on the strength, purity, quality, and package integrity of the sterile product.

Inspection actions should include:

- Determine what type of sterilization cycles are used (bioburden based or overkill).

- Review validation / revalidation / or periodic evaluation of terminal sterilization cycles for representative types of products.

- For selected products, verify that the parameters and loading patterns used in production are the same as those used in validation studies.

- Determine the minimum acceptable cycle allowed in the SOP (as opposed to the nominal or routine cycle) and compare that to the validated cycle (using BI) to verify it has been properly qualified.

- Determine how sterilization cycles are documented, monitored, and reviewed.

- Review deviations or atypical data from sterilization operations that indicate inconsistencies in process performance.

vii. Parametric Release of Terminally Sterilized Drug Product

Parametric release is defined as a sterility assurance release program based on demonstrated control of the sterilization process. It enables a firm to use defined critical process control data, in lieu of the sterility test to fulfill the intent of 21 CFR 211.167(a). The firm should have a sterility assurance program in place that encompasses multiple, integrated CGMP systems that are in a state of control, including (1) sterilization process validation and control, (2) verification by load monitor(s), (3) a validated container closure system, and (4) an effective quality system. If using moist heat verify that the conditions described in FDA's Compliance Policy Guide Section 490.200, *Parametric Release – Drug Products Terminally Sterilized by Moist Heat,* are met.

viii. Inspection of Injectable Products

This area covers 100% inspection of injectable products including: cracks in the primary container, visible particles, and other significant defects.[28] Inspection actions should include:

- Verify the firm has written procedures that define the defects that cause a container to be removed from the lot and actions to take if the number of defects exceeds a pre-determined level. Types of defects should be comprehensive.
- Significant defect categories should be identified. Results of inspection of each batch should be compared to established action levels.
- Evaluate the appropriateness of and the rationale for pre-determined action levels.
- Evaluate the firm's investigation into the cause of rejects, including units rejected for cracks and visible particulates.
- Observe the inspection process, including product inspection, including visual inspection of in-process or final product bulk solution, commercial product used for production, and finished product.
- Challenge visual/manual inspection rates through observation.
- Evaluate the adequacy of written procedures for visual inspection.
- Evaluate personnel qualification and requalification and equipment qualifications according to established procedures. Evaluate personnel qualification including the use of reference samples for qualification.

[28] See the draft guidance for industry *Inspection of Injectable Products for Visible Particulates* (December 2021). When final, this guidance will represent the FDA's current thinking on this topic.

- If a manual system is used, determine if employees are trained and qualified to verify that they can recognize and remove defects under actual or simulated production conditions.

- If an automated or semi-automated system is used, determine the equipment is qualified and the software program or equipment settings have been validated for all types of products being inspected (e.g., clear vials, amber vials, colored solution, suspensions). If the equipment is an automatically controlled computer-based system, an assessment of the system and validation is warranted.

- Evaluate the firm's program for sampling and examination of inspected containers and evaluate the effectiveness of inspection and action taken if the reject level is reached.

- Evaluate the firm's assessment of units rejected during filling operations (any separate inspection prior to the 100% inspection stage), established alert/action limits, and investigations performed where appropriate.

ix. Personnel (Gowning, Training, Aseptic Techniques)

The type of gowns and personal protective equipment worn by employees shall be appropriate for the areas in which they work. There should be detailed written procedures that describe the gowning requirements for each processing area. Evaluate the following:[29]

- For aseptic processing, determine whether the gowns (which typically include face masks, hoods, protective goggles, gloves, and boots) are sterilized and made of non-particle shedding material. Ensure that the gowns cover all skin, hair, and facial hair.

- Review how the incoming sterile gowns/garb are accepted or rejected for use.

- Evaluate the firm's program for training, testing, and qualifying and re-qualifying employees who work in the controlled areas, especially those who set up and operate aseptic processing lines.

- Evaluate the aseptic techniques of employees by observing aseptic processing operations.

- For selected employees, verify the training, testing, qualifying, and re-qualifying were done as specified in procedures.

[29] See Section IX.A of the guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process* (October 2004) and the draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). When final, this guidance will represent FDA's current thinking on this topic. See also PDA Technical Report No. 28, revised 2006, Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals, and PDA Technical Report No. 22, revised 2011, Process Simulation for Aseptically Filled Products.

- Verify the training is done on a continuing basis.

x. Batch Records

Master batch records should be comprehensive and thorough, with all process steps including in-process controls accounted for. Production batch records must provide complete documentation of the production of each batch of a drug product. The actual batch output (yield) must be compared to the projected (calculated) output for each drug product. If the actual output is different than expected after accounting for sampling and known process loss, this finding should be considered an indicator of a potential problem with production and must be investigated. An acceptance level for actual output should be established that ensures batch-to-batch consistency. Failure to meet the acceptance criteria and production standards must be investigated before making the batch disposition decision and may require that the batch be rejected. Inspection actions should include:

- Review of environmental and personnel monitoring data, as well as other data relating to acceptability of support systems (e.g., HEPA/HVAC, WFI, steam generator) and manufacturing equipment. This review is considered essential to batch release decisions. The batch record should include documentation that assures this type of holistic review is done before the release of a lot for distribution.

- For aseptic processing, verify interventions into critical areas (Class 100/ISO 5) are documented so they can be reviewed and evaluated by the quality unit.

- Review batch records to verify they include complete information for all sterilization processes.

(e) Packaging and Labeling System

Packaging of non-sterile and sterile drugs must be appropriate to the product and capable of ensuring the integrity and sterility, if applicable, of the product until it is administered to a patient. Labels must contain required information, and labeling operations must include controls to prevent mix-ups; furthermore, procedures must be developed to ensure these requirements are met. The following aspects of packaging and labeling are critical to ensure the quality of compounded drug products and must be implemented by Outsourcing Facilities:

- The container, closure, and packaging systems provide adequate protection against foreseeable external factors in storage, shipment, and use that could cause contamination or deterioration of the finished drug product (e.g., cracked vials, leaks in bags). A container closure integrity study may be required to ensure the container closure is suitable.

- Adequate controls should be established for issuing labels, examining issued labels, and reconciliation of used labels to prevent mix-ups.

- Controls are in place for maintaining adequate separation between the labeling and packaging operations of different products, including ones with different strengths or containers or closures, to prevent mix-ups.

- Adequate controls have been established to ensure proper identification of any filled containers of non-sterile or sterile drug products that will be stored unlabeled for any period.

- Packaging records include results of examinations of all labels used and specimens of all labeling used are retained as part of packaging records.

- The labeled finished drug product has been examined for accuracy before release.

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[30] below should be covered:

- 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

- Adequate packaging records that include specimens of all labels used

- Control of issuance of labeling, examination of issued labels, and reconciliation of used labels

- Examination of the labeled finished product

- Adequate inspection (proofing) of incoming labeling

[30] The depth of coverage may vary depending upon inspectional findings.

- 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 / Beyond Use Date (BUD) dates on the label
- Validation of packaging and labeling operations including validation and security of computerized processes
- Documented investigation into any unexpected discrepancy

Areas of special concern for sterile products include:

- Determine that packaging and labeling operations do not introduce risk to product integrity (for example, damage to the container or closure that could affect the integrity of the unit).
- Determine that the container, closure, and packaging systems provide adequate protection against foreseeable external factors in storage, shipment, and use that can cause contamination or deterioration (e.g. cracked vials during shipment if not properly protected; pinhole leaks in bags or frozen drug products; tears or holes in overwraps of sterile bulk antibiotics and large volume parenterals; and unseating of stoppers in aluminum cans containing sterile bulk APIs due to pressure changes during shipment by air).
- The firm must have adequate controls to always ensure proper identification of unlabeled product (e.g., when unlabeled components or unlabeled finished products are staged or stored awaiting labeling or further processing, there should be a system in place to ensure product mix-ups do not occur).
- Tracking of refrigerated or temperature-controlled units for room temperature exposure times (e.g., warm up of refrigerated units prior to label application).
- Tracking and investigation (as specified and appropriate) of rejected units culled during packaging and labeling operations.

(f) Laboratory Control System

This system includes activities related to testing, analytical methods, laboratory procedures and the stability program. [31] The principal objective of a laboratory control system is to ensure all testing and laboratory control mechanisms are designed and followed to confirm drug products have the identity, strength, quality, and purity they purport or are represented to possess. Whether using compendial or alternative analytical testing methods, it is imperative that all methodologies have been demonstrated to be suitable for the drug products for which the method is used as either a quantitative or qualitative test or both. Whether a validated test or an established compendial test (compendial tests are considered validated) is used, the test has been verified and documented. If using a validated or an established compendial test procedure in a specification, the test has been verified and documented to work under the conditions of actual use. The purpose of validation for a non-compendial method is to ensure the method is suitable for its intended purpose and can produce valid results. When a method is used for quantitation of drug components, accuracy, precision, specificity linearity, and range should be established. For other determinative tests, limits of quantitation and detection may also need to be established. All specifications, standards, sampling plans, and test procedures should be scientifically sound and appropriate.

Each Outsourcing Facility is expected to have written and approved procedures, and documentation for any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms. 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.

The inspectional evaluation of this system should include the following:

- Adequacy of staffing, equipment (including suitability), and facility, for all laboratory operations conducted onsite.
- Calibration and maintenance programs for analytical instruments and supporting equipment
- Validation and security of computerized or automated processes
- Reference standards; source, qualification, storage (if not a compendial standard: purity and assay, and tests to establish equivalency or superiority to current official reference standards as appropriate)

[31] USP General Chapter <51> Antimicrobial Effectiveness Testing, USP General Chapter <61> Microbial Examination of Non-sterile Products, USP General Chapter <62> Microbial Enumeration of Non-sterile Products: Tests for Specified Microorganisms, USP General Chapter <71> Sterility Test, USP General Chapter <788> Particulate Matter in Injections, USP General Chapter <789> Particulate Matter in Ophthalmic Solutions, USP General Chapter <790> Visible Particulates in Injections, USP General Chapter <771> Ophthalmic Products—Quality Tests, USP General Chapter <1207> Package Integrity Evaluation—Sterile Products, Pyrogens and Endotoxins Testing

- System suitability checks on chromatographic systems (e.g., Gas Chromatography or High-Performance Liquid Chromatography) and other systems (e.g., Fourier Transform Infrared Spectroscopy) where appropriate
- Specifications, standards, and representative sampling plans
- Adherence to the written methods of analysis for each test, and all results documented
- Validation and verification of analytical methods
- For compendial methods, documentation that the test was verified under the conditions of actual use
- For analytical methods validated at another site, method transfers are conducted to ensure accurate transfer of the development, qualification, and operating parameters for the method
- Control system for implementing changes in laboratory operations
- Unauthorized access and unauthorized modification of all systems and data
- Sample identified uniquely, and chain of custody maintained and documented
- Complete analytical records from all tests performed to ensure compliance with established specifications and standards, including examinations and assays along with summaries of results
- Quality and retention of raw data (e.g., chromatograms and spectra)
- Data integrity controls (i.e., audit trails, controlled documents, methods, procedures, worksheets, and lab notebooks)
- Correlation of result summaries to raw data; preservation of unused data
- Adherence to an adequate OOS procedure which includes timely completion of the investigation
- Adequate reserve samples[32]; documentation of reserve sample examination
- Stability testing program (including demonstration of stability-indicating capability of the test methods utilized to establish stability of drug product and all relevant product quality attributes)

[32] See the draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). When final, this guidance will represent FDA's current thinking on this topic.

- Documented investigation into any unexpected discrepancy
- Training/qualification of personnel

i. Release Testing

Appropriate specifications must be established for each drug product either by following compendial monographs, or if no monograph is applicable, through scientifically sound and appropriate evaluation. Established specifications should address those attributes necessary to ensure the quality of the finished drug product. Generally, these include, where applicable: identity, purity, color clarity, pH, content uniformity, and microbial testing. Additionally, for sterile products, sterility testing is a CGMP requirement, and bacterial endotoxins and particulate testing may also be applicable. However, specifications for bacterial endotoxins and particulates are dependent on the intended dosage form of the finished drug product as well as the intended route of administration. Testing of other quality attributes (for example: disintegration and dissolution-testing) may be necessary depending on the dosage form. Where a compendial monograph is applicable, other special tests and specifications may apply such as impurity testing. FDA has stated through published guidance certain regulatory exemptions regarding certain release testing requirements.[33]

Where appropriate, drug products containing antimicrobial preservatives or antimicrobial agents (self-preserving) should be evaluated for antimicrobial effectiveness - See USP General Chapter <51> Antimicrobial Effectiveness Testing for more information. Alternatively, other studies or testing may be acceptable in lieu of a full antimicrobial effectiveness study.[34]

ii. Stability

An appropriate stability program must be established for all marketed drug products to assess the stability characteristics of each finished drug product and the results of such testing used to determine storage conditions and expiration dates (or BUD) to ensure the drug product will retain its quality and remain sterile through the labeled expiration date.

Because some compounded drugs produced by Outsourcing Facilities have small batch sizes and less frequency of production than approved drug products, FDA generally does not intend to take regulatory action regarding certain requirements with respect to certain CGMP requirements in parts 210 and 211 regarding stability testing.[35]

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[33] See the draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). When final, this guidance will represent FDA's current thinking on this topic.

[34] See the draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). When final, this guidance will represent FDA's current thinking on this topic.

[35] See the draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). When final, this guidance will represent FDA's current thinking on this topic. For more information on repackaged drugs by Outsourcing Facilities see the guidance for industry *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities* (January 2017).

However, in the case of no stability studies or reduced testing for products that meet certain criteria, a container closure integrity test should still be used to establish the integrity of the container closure system and the sterility of the product over the labeled shelf life. Additionally, for products labeled as multidose, specifications that assure that the product is adequately self-preserving, or for products containing antimicrobial preservatives, antimicrobial effectiveness testing is performed to ensure antimicrobial activity is effective over the labeled shelf life.

iii. Contract Testing Laboratory

If contract testing laboratories are utilized by an Outsourcing Facility to perform drug testing (or any components and in-process materials), all or in part, the Outsourcing Facility's quality control unit is responsible for approving and rejecting drugs tested by the contractor. Also, the contract testing lab should be qualified by the Outsourcing Facility prior to relying on the services of the contract lab. The Outsourcing Facility is responsible for ensuring the contract testing laboratory conforms to CGMP. The contract testing laboratory should have documentation that whether using compendial or alternative analytical testing methods, all methodologies have been demonstrated to be suitable for the drug products for which the method is used. Whether a validated test or an established compendial test is used, the test has been verified and documented, as appropriate. The following should be evaluated when a contract lab is utilized:

- Sharing of reports of analysis, investigations, and laboratory discrepancies.
- A system for notification of OOS results (e.g., electronic notification, autogenerated or manual), timeliness of notification of OOS; laboratory investigations reviewed before OOSs are invalidated.
- Routine auditing to ensure the contract testing lab remains in a controlled state in accordance with CGMP.
- Designation of all relevant responsibilities (the Outsourcing Facility's quality control unit should be responsible for final release or rejection).

B. Sampling

Samples may be collected to document suspected contamination, adulteration, or misbranding encountered during an inspection. Official samples may consist of finished drug product, raw materials, and/or components. Official samples are not necessary to document a 501(a)(2)(A) or 501(a)(2)(B) adulteration charge. Documentary samples may be submitted when the documentation illustrates the deficiencies and to obtain evidence of interstate shipment. OII 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. If the

Division believes that either official samples or environmental monitoring sampling are warranted, please contact CDER/OC/OCQC/DCI.[36]

C. Inspection Teams

An inspection team (see IOM section 5.2.8 – Team Inspections) composed of experts from within OII Divisions, or Headquarters is encouraged when it provides needed expertise and experience. If technical assistance is needed, contact OII Compounding. OII leads the inspection with CDER participation when requested. 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.

2. **Reporting**

If OII observes critical conditions (e.g., those which may result in an imminent health hazard), as appropriate and if feasible, they can be discussed between OII and CDER/OCQC before the inspection closes. The OII management representative or designee, the investigator(s), and CDER/OCQC 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 5.7 – Reporting for guidance in reporting of inspectional findings. Identify systems covered in the Summary of Findings. 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.

[36] For sampling guidance, refer to IOM, Chapter 4 – Sampling.

PART IV—ANALYTICAL

1. 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, Non-sterile examination
- Other microbiological examinations
- Particulate Matter in Injectables

Email OCS/OARL at OCOCSOARLProgramCoordinators@fda.hhs.gov for servicing laboratories for chemical and microbiological testing. When contacting OARL 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 Dashboard is not sufficiently detailed to accurately identify laboratories and should not be used for selecting servicing laboratories under this compliance program.

2. Analyses to be Conducted

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 OCS/OARL.

- The presence of cross-contamination must be confirmed by a mass spectroscopic method.
- Ensure the analysis for the dissolution rate is performed by a second dissolution-testing laboratory.
- Microbiological examinations should be based on appropriate sections of USP and Pharmaceutical Microbiology Manual.

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 OII's assessment of the significance of the CGMP deficiencies.

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 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 OCQC. These approaches may range from shut down of operations, recall of products, conducting testing programs, development of new procedures, modifications of facilities and equipment, to simple immediate corrections of conditions. 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.

Requests and review of records, documents, and other information from RRA activities may reveal potentially violative practices. In such cases, OCQC's evaluation of an OAI 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 comply 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 OCQC. When deciding the type of action to recommend, the initial decision should be based on the seriousness or frequency of the problems.

PART VI—REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

1. **References**

A. Code of Federal Regulations, Title 21

- 21 CFR Part 210
- 21 CFR Part 211

B. Compliance Programs

- CP 7356.002—Drug Manufacturing Inspections.
- CP 7356.002A—Sterile Drug Process Inspections
- CP 7356.021—Drug Quality Reporting System (DQRS) (MedWatch Reports); NDA Field Alert Reports

C. FDA Guidances

- Guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process* (October 2004)
- Guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (October 2006)
- Draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020)[37]
- Draft guidance for industry *Inspection of Injectable Products for Visible Particulates* (December 2021)[38]

D. ICH Guidances

- ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023)
- ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009)

E. Other Procedures and References

- Investigations Operations Manual, section 5. 1.2–Inspectional Approach
- Investigations Operations Manual, Chapter 5, Section 5.5.10 – Reports of Observations for further guidance on the content of Inspectional Observations.
- Inspection Guide, Lyophilization of Parenteral (7/93)
- ISO 14698 Cleanrooms and Associated Controlled Environments Biocontamination Control

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

- PDA Technical Report No. 1 (Revised 2007) Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control; and ISO 17665 Moist Heat Sterilization.
- PDA Technical Report 51 (2010), Biological Indicators for Gas and Vapor Phase Decontamination Processes: Specifications, Manufacture, Control and Use.
- RABS for Aseptic Processing, ISPE (August 2005).

2. **Attachment**

- Attachment A: Examples of Indicators of an Advanced Quality System

3. **Program Contacts**

A. For Enforcement-Related Guidance or Policy

For enforcement-related guidance or policy, including evidence needed and sufficiency, citations, and inspection endorsement advice, please send an email to the following address: OIICompounding@fda.hhs.gov

B. For 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 : OPQPolicy@fda.hhs.gov with a copy to CompoundingInspections@fda.hhs.gov.

4. **Acronyms**

API: Active Pharmaceutical Ingredient

CMS: Compliance Management System

DQRS: Drug Quality Reporting System

CAPA: Corrective Action and Preventive Action

EIR: Establishment Inspection Report

CDER: Center for Drug Evaluation and Research

FAR: Field Alert Report

CGMP: Current Good Manufacturing Practice

FMD: Field Management Directive

ICH: International Council for Harmonisation

IOM: Investigations Operations Manual

NAI: No Action Indicated

OAI: Official Action Indicated

OARL: Office of Analytical and Regulatory Laboratories

OC: Office of Compliance

OCS: Office of the Chief Scientist

OII: Office of Inspections and Investigations

OMQ: Office of Manufacturing Quality

OOS: Out-of-Specification

OPMA: Office of Pharmaceutical Manufacturing Assessment

OPQ: Office of Pharmaceutical Quality

PAC: Product/Assignment Code

PET: Positron Emission Tomography

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 OII RESPONSIBILITIES OVERVIEW

CDER and OII roles and responsibilities for surveillance and surveillance-related for-cause inspections subject to this compliance program are summarized below.

1. **Surveillance Inspection Responsibilities**

Once an Outsourcing Facility is registered with FDA, the facility will be added to the list of facilities FDA intends to inspect according to a risk-based schedule. In accordance with this compliance program, OII schedules and leads surveillance inspections of Outsourcing Facilities, with CDER participation as appropriate. OII will conduct an assessment to review the facts before determining an initial classification. CDER will conduct a compliance assessment to review the facts before progressing with any regulatory action per established procedures. Typically, the assessment will be based upon review of the Form FDA 483, and other pertinent exhibits and documents. The review of information requested to be collected under this compliance program may identify additional violations not documented on the Form FDA 483.

2. **Reinspection Responsibilities**

Requests for reinspections are initiated by OCQC. Once OCQC determines a reinspection is warranted, the office prepares an assignment memo that sets forth the areas of required coverage, which may include surveillance program coverage. OII reviews the assignment, and if accepted, schedules the inspection. OII leads establishment reinspections with CDER participation, as appropriate.

OII will conduct an assessment to review the facts before determining an initial classification. CDER will conduct a compliance assessment to review the facts before progressing with any regulatory action per established procedures. Typically, the assessment will be based upon review of the Form FDA 483, and other pertinent exhibits and documents. The review of information requested to be collected under this compliance program may identify additional violations not documented on the Form FDA 483.

3. **For-Cause Inspection Responsibilities**

Requests for for-cause inspections are initiated by OCQC. Once the OCQC 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. OII reviews the assignment, and if accepted, schedules the inspection. OII leads for-cause inspections with OCQC participation, as appropriate.

OII will conduct an assessment to review the facts before determining an initial classification. CDER will conduct a compliance assessment to review the facts before progressing with any regulatory action per established procedures. Typically, the assessment will be based upon review of the Form FDA 483, and other pertinent exhibits and documents. The review of information requested to be collected under this compliance program may identify additional violations not documented on the Form FDA 483.

ATTACHMENT A—EXAMPLES OF INDICATORS OF AN ADVANCED QUALITY SYSTEM

Outsourcing Facilities can demonstrate practices that are indicative of mature quality practices that, if effectively implemented, provide the foundation for exceeding CGMP requirements. Examples may include a steadfast focus on implementing continual improvements, using the latest innovations to enhance control, and creating a culture of quality where leadership demonstrates a commitment to quality and promotes employee engagement and empowerment. Indicators of a more advanced quality system may inform FDA's risk-based approach to plan Outsourcing Facility inspections.

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 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.

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.