Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmaceutical Quality/Manufacturing Standards (CGMP)

Revision 2

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TABLE OF CONTENTS

Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes FDA's policies regarding compliance with current good manufacturing practice (CGMP) requirements for facilities that compound human drugs and register with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 501(a)(2)(B) of the FD&C Act, a drug is deemed to be adulterated if it is not produced in accordance with CGMP. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211.[2] 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. This guidance provides for conditions under which FDA generally does not intend to take regulatory action against an outsourcing facility regarding certain CGMP requirements in parts 210 and 211 during this interim period. This guidance applies to drugs compounded in accordance with section 503B. In addition, this guidance generally applies to drugs that outsourcing facilities repackage and biological products that outsourcing facilities mix, dilute, or repackage in accordance with relevant guidance for outsourcing facilities.[3]

This guidance reflects FDA's intent to recognize the differences between outsourcing facilities and conventional drug manufacturers, while maintaining the minimum standards necessary to

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research and in cooperation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] Positron emission tomography (PET) drug products are subject to CGMP regulations at 21 CFR part 212 and are not covered by this guidance.

[3] See guidances for industry *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities* and *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* (Biologics guidance). To the extent that the policies in the Biologics guidance differ from this guidance (e.g., conditions concerning assigning a beyond-use date to repackaged biological products based on stability testing), the policies described in the Biologics guidance apply. FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

protect patients from the risks of contaminated or otherwise substandard compounded drug products.

This guidance revises the draft guidance *Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* issued in July 2014. Revision 1 was developed to (1) include considerations for non-sterile compounded drug products; (2) differentiate between requirements applicable to sterile compounded drug products and non-sterile compounded drug products where appropriate; (3) include changes regarding stability testing, including the assignment of a beyond-use date (BUD) as an expiration date, and release testing requirements; and (4) address reserve samples and provide guidance on "in-use times." Revision 2 refines a description of antimicrobial effectiveness testing in section III.K. and clarifies that section C of appendix B does not apply to non-sterile unpreserved aqueous drug products.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Drug Quality and Security Act added a new section 503B to the FD&C Act.[4] Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded in an outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act,[5] the requirement to label drug products with adequate directions for use under section 502(f)(1) of the FD&C Act,[6] and the drug supply chain security requirements in section 582 of the FD&C Act,[7] 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 CGMP requirements under section 501(a)(2)(B) (see section 503B).

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 . . . .

[4] See Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587–588 (2013).

[5] 21 U.S.C. 355.

[6] 21 U.S.C. 352(f)(1).

[7] 21 U.S.C. 360eee-1.

Further, section 501 of the FD&C Act, as amended by the Food and Drug Administration Safety and Innovation Act,[8] 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 requirements for finished drug products, except PET drug products, are established in 21 CFR parts 210 and 211. The primary focus of this guidance is on those aspects of part 211 that relate to sterility assurance of sterile drug products and the safety of both sterile and non-sterile compounded drug products more generally, including with respect to strength (e.g., subpotency, superpotency), and labeling or drug product mix-ups, because these aspects of outsourcing facility operations pose the highest risk to patient safety if not conducted properly.

The recommendations in this guidance are consistent with the principles of good manufacturing practice, which hold that quality is best assured by implementing appropriate controls throughout the manufacturing process, with end-product testing providing additional assurance. This guidance also provides a risk-based approach to CGMP requirements. Accordingly, this guidance focuses on control of raw materials, facility design and maintenance, production techniques and controls, and personnel practices as the most critical aspects of ensuring quality for all drug products. Other CGMP requirements, such as testing samples of the finished drug product before batch release and the collection of reserve samples, provide additional assurance of drug quality and are described with respect to higher risk outsourcing facility operations. For example, the guidance distinguishes, where applicable, between higher risk compounding activities (e.g., higher volume of production for a drug product, sterile production, manual manipulations) and lower risk compounding activities (e.g., lower volume of production, non-sterile production, use of automated equipment).

Depending on the level of risk, the guidance describes certain conditions under which FDA generally does not intend to take regulatory action against an outsourcing facility regarding specific CGMP requirements.

III. CGMP FOR OUTSOURCING FACILITIES

A. Quality Assurance Activities

Quality assurance activities are needed to ensure that procedures are followed and a quality drug product is produced (see, e.g., §§ 211.22, 211.180, 211.192, 211.198). Part 211 (see, e.g., § 211.22) requires that drug producers establish a quality control unit to oversee various aspects of production, including strength as well as sterility assurance activities for sterile products and microbiological quality for non-sterile products.

[8] Pub. L. No. 112-114, 126 Stat. 993 (2012).

The quality control unit should be independent; that is, the quality control unit should not take on the responsibilities of other units of the outsourcing facility's organization, such as those handled by production personnel, in order to preserve the integrity of the quality control unit's functions. FDA has found that quality control units that are independent from other operations are more likely to be able to fulfill their required functions.[9] FDA recommends the staffing level be adequate to perform all quality assurance functions at a level commensurate with the scale of the compounding operation, including number and volume of drug products compounded.

Procedures describing the role and responsibilities of the quality control unit must be established and followed (§ 211.22(d)). The following aspects of quality assurance and quality control are critical to ensuring the quality of compounded sterile and non-sterile drug products at outsourcing facilities.

The quality control unit is responsible for ensuring that each batch of finished drug product is sampled and tested to ensure that it meets appropriate specifications for release (see §§ 211.22(a), 211.165(d)). For sterile products, procedures should be established and followed to ensure that for each batch intended to be released without completed sterility testing (see section I and Appendix A), the results of the sterility testing, once available, are reviewed and added to the batch record (see § 211.188).

The quality control unit must periodically (at least annually) review records of compounding operations to evaluate the quality standards for each drug product to determine the need for changes in specifications or control procedures (§ 211.180(e)). As part of this review, the quality control unit should identify trends and evaluate quality indicators such as (where required by part 211):

- Results of environmental monitoring.
- Results of personnel monitoring.
- Where water is used as a component in the drug product, results of water system testing for water that is purified/processed on-site, or if water is purchased as an incoming component, testing results from the supplier or results of testing conducted by the outsourcing facility.
- Results of finished drug product testing.
- All media fills/process simulations performed since the last review.
- Periodic scrutiny of operations to ensure adherence to procedures and proper aseptic technique.

[9] FDA inspection information indicates that most outsourcing facilities maintain personnel in a quality control unit that is fully separate from compounding operations. However, FDA recognizes that there may be an extraordinary circumstance in which an individual in the quality control unit may need to participate in another operation. In such circumstances, that person is still accountable for implementing all of the controls and reviewing compounding operations to ensure that facility, process, and product quality standards have been met. See § 211.22.

- Complaints, discrepancies, failures, and yield variation.

The quality control unit is responsible for discrepancy and failure investigations and the development and oversight of effective corrective actions, which also include changes necessary to prevent recurrence, regarding the following (see, e.g., §§ 211.192, 211.180(e)):

- Results of tests and examinations, regardless of batch disposition, if applicable to evaluate the quality of components, containers, closures, in-process materials, and finished product. Examples of such tests and examinations include but are not limited to sterility testing, endotoxin levels, content assay, impurity assay, particulate matter, reconstitution time, content uniformity, preservative content testing, microbial enumeration, tests for specified microorganisms, and, weight, volume, or counts.

- Unexpected results (e.g., potential defects) or trends.

- Failures that occur during validation or revalidation. These could include process validation, sterilization, or depyrogenation processes, including media fill/process simulation failures, as applicable.

- Stability failures, including failures of quality that are determined to have causes other than degradation of the drug product.

- Environmental and personnel monitoring results that exceed alert or action limits.

- Process deviations or equipment malfunctions that involve critical equipment, such as sterilizers, lyophilizers, pellet machines, capsule machines, mixers, and homogenizers.

- Complaints that indicate possible drug product contamination or other potential risks to patients (e.g., hazy or cloudy drug product, foreign matter/particulates in injectable drug products, cracked or leaky containers, change in color or appearance, particles falling out of oral solutions).

B. Facility Design

Part 211 sets out the requirements applicable to the design of facilities used in the manufacture, processing, packing, or holding of a drug product (see, e.g., § 211.42). The design of a facility should consider the products produced and must provide the necessary level of control to prevent mix-ups and contamination (§ 211.42).

The production areas in which components, drug products, in-process materials, equipment, and containers or closures are prepared, held, or transferred must be designed to minimize the level of contaminants so as to prevent objectionable microorganisms in non-sterile drug products (see § 211.113(a)) and prevent microbiological contamination of drug products purporting to be sterile (see § 211.113(b)). Processing and controlled areas must be clean and sanitary (§ 211.56).

Additional Considerations for Sterile Drug Products

Outsourcing facilities should meet the following elements:

- Sterile drugs should be produced only in ISO 5 or better air quality as determined under dynamic conditions (see Table 1 for International Organization for Standardization (ISO) cleanroom classification standards).

Table 1. ISO Classification of Particulate Matter in Room Air[*]

ISO Class Name	Particles/m^3
3	35.2
4	352
5	3,520
6	35,200
7	352,000
8	3,520,000

[*]Limits are in particles of 0.5 µm and larger per cubic meter (current ISO) measured under dynamic conditions. Adapted from ISO 14644-1:2015, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.

- The facility should be designed and operated with cascading air quality (e.g., by proper air classification and air pressurization) to protect the ISO 5 zone (or critical area[10]). The facility layout, room separation, and process flow must be designed to prevent the influx of contamination from adjacent areas and rooms of lower air quality and to avoid any disruption of HEPA unidirectional flow (§ 211.42).

- The air cleanliness classification of the area surrounding the ISO 5 zone immediately adjacent to the aseptic processing line should, at a minimum, meet ISO 7 standards under dynamic conditions.

- If an isolator[11] is used, the surrounding area should, at a minimum, meet ISO 8 standards under dynamic conditions.

- If a restricted access barrier[12] is used (e.g., a glove box), the surrounding area should, at a minimum, meet ISO 7 standards under dynamic conditions.

- Terminally sterilized drugs should be produced in ISO 8 or better air quality as determined under dynamic conditions.

[10] A *critical area* is an area designed to maintain sterility of sterile materials. See guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.

[11] An *isolator* is a decontaminated unit supplied with ISO 5 or higher air quality that provides uncompromised, continuous isolation of its interior from the external environment. For further information, see also guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.

[12] See guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice.*

The ISO 5 zone or critical area must be qualified (i.e., shown to meet the specifications; see §§ 211.42, 211.113(b)). Qualification should include at least the following studies and tests, which must be documented as having been conducted (see § 211.113(b)), including the particular conditions under which the studies and tests were conducted:[13]

- Airflow studies (e.g., an in-situ smoke study) should be conducted under simulated operational conditions to evaluate airflow patterns because of the risk for contamination of exposed product in the critical area. These studies should be conducted at the critical area to demonstrate unidirectional flow and sweeping action over and away from the product under dynamic conditions and should be repeated when any changes are made to the critical area that might affect airflow.[14] Because proper control of airflow is necessary to prevent contamination, any indication of poor air control (e.g., non-unidirectional, turbulent) must be corrected before use (see §§ 211.42, 211.113(b)).

- HEPA periodic testing/recertification should be performed at least twice a year to ensure that appropriate airflow and quality are maintained. These tests should include integrity testing of the HEPA filters, particle counts, and air velocity checks.

- Velocities of unidirectional air should be measured 6 inches from the HEPA filter face and at a defined distance close to the work surface in the ISO 5 area.

- If any portable ISO 5 units are moved from one location to another, requalification of the unit should be performed before resuming sterile compounding.

C. Control Systems and Procedures for Maintaining Suitable Facilities

To prevent contamination or mix-ups during the course of operations, § 211.42 requires separate or defined areas or other similar control systems for a facility's operations.[15] Section 211.56 requires that procedures be established and followed that assign responsibility for sanitation and describe in detail the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

For multiuse facilities and nondedicated equipment, changeover and cleaning procedures for equipment and utensils must be established and followed to prevent contamination, including cross-contamination between products (see §§ 211.42, 211.67).

Procedures for cleaning and disinfecting must also be established (see §§ 211.42, 211.56, 211.67). Equipment surfaces that come in contact with drug products, containers, or closures must be cleaned at appropriate intervals to prevent contamination (see § 211.67). The suitability

[13] In addition to documenting these tests and studies, the CGMP regulations generally require that other key activities be documented (see part 211, subpart J: Records and Reports).

[14] Additional information may be found in NSF/ANSI 49—2014 Biosafety Cabinetry: Design, Construction, Performance, and Field Certification.

[15] For example, this would be especially critical when using powders because powder particles can become airborne and contaminate other areas unless airflow is designed to contain such particles.

and efficacy of the cleaning agents and cleaning methods should be evaluated, and the cleaning agent's compatibility with applicable work surfaces should be assessed. Published literature and supplier certificates of analysis (COAs) 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. The expiration dates of cleaning and disinfection agents should be closely monitored and expired solutions should be discarded.

For non-sterile drug production, water used as a final rinsing agent for any equipment or utensils that come in direct contact with the drug product should meet the requirements for Purified Water, USP, or higher quality standards.[16]

If powder drugs are handled, procedures must be established and followed to appropriately manage cross-contamination risk (see § 211.100). This is particularly important if the powder is cytotoxic or highly sensitizing. FDA recommends the physical segregation of areas in which powder drugs are exposed to the environment. For penicillin products, a separate facility is required (see § 211.42(d)). However, FDA has clarified that separate buildings may not be necessary, provided that the manufacturing operation involving penicillin is isolated (i.e., completely and comprehensively separated) from the areas in which non-penicillin products are manufactured.[17] For non-penicillin beta-lactam products, FDA recommends complete and comprehensive separation from other products.[18] Additionally, appropriate controls related to movement of equipment, product, and personnel should be established to prevent cross-contamination of non-beta-lactam products.

In general, processes and procedures at an outsourcing facility should minimize contamination risks posed by, for example, the number and complexity of manipulations, number of simultaneous operations and workstations, and staging of materials used in the process.

Additional Considerations for Sterile Drug Products

HEPA filters should be qualified to provide appropriate air quality and be periodically maintained and tested to ensure intended air quality. Discolored, dirty, or damaged HEPA filters should be repaired or replaced.

Temperature and humidity must be maintained in cleanroom areas; such controls are critical to reduce microbiological growth (see § 211.46). A specification for humidity should be established considering that higher humidity supports microbial growth, while too little humidity can cause problems with static electricity (which may be particularly problematic when working with powders) and may lead to increased particulates. Cleanroom temperature and humidity specifications should be maintained solely through the facility's central heating, ventilation, and

[16] See FDA's *Guide to Inspections of High Purity Water Systems* at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/high-purity-water-system-793.

[17] Preamble to the final rule, "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding." 43 FR 45014, at 45038 (September 29, 1978).

[18] See guidance for industry *Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination*.

air conditioning (HVAC); peripheral devices such as stand-alone (de-)humidifiers and air conditioners should not be used because they generate airborne particles, are water sources, and may harbor microorganisms. As a scientific matter, a system for environmental monitoring must include the establishment of pressure differential limits (see § 211.42), and control systems should include built-in alarms to detect excursions. An adequate control system includes monitoring for pressure differentials, humidity, and temperature during production and taking prompt action to correct adverse conditions, which are necessary activities to prevent contamination during aseptic processing (see §§ 211.42, 211.46, 211.58). If a problematic condition cannot be immediately corrected, production should stop until it has been corrected. Regardless of whether production is stopped or allowed to continue, the impact of any excursions on product that is already in process should be evaluated. Among other requirements in § 211.192, any unexplained discrepancy must be investigated, the results of which must be documented.

Monitoring procedures should require documentation and investigation of any instances in which there is a loss of positive pressure in the cleanroom during actual production and documentation of the batches affected and the corrective action taken. These checks should be conducted regularly on a schedule that considers the environment, such as use of an isolator versus a less protected process, and the results should be recorded in logs and evaluated against prespecified alert and action limits at each check.

In addition to the requirements in §§ 211.42 and 211.56, FDA recommends that outsourcing facilities ensure that air vents and airflow are not obstructed—by large equipment, for example—in such a way that could potentially compromise aseptic operations. Equipment that is not needed for the specific cleanroom operations conducted should not be stored in the cleanroom.

Procedures for cleaning and disinfecting ISO 5 areas/units should include detailed instructions for consistently and properly cleaning and disinfecting surfaces that are difficult to access. A system for cleaning and disinfecting all critical areas to produce aseptic conditions includes sporicidal and other sterile disinfectants and lint-free sterile wipes (see § 211.42). Procedures must describe the methods and schedule for cleaning (see §§ 211.42, 211.56, 211.67, 211.182) and should include the use of sporicidal disinfectants in the ISO 5 area and other classified areas on a regular basis.

Water used as a cleaning or rinsing agent for any equipment or utensils that will not be subsequently disinfected or sterilized and depyrogenated must be sterile (see § 211.113(b)). Purified Water, USP, is considered acceptable for use with equipment or utensils that will be sterilized and depyrogenated.

Based on the results of environmental monitoring (see section D below), the disinfection program must be revised if there are indications that the frequency of disinfection or the methods or type of disinfectant(s) used are inadequate to ensure appropriately clean surfaces (see §§ 211.42, 211.56, 211.67, 211.113). Conducting disinfectant effectiveness testing may be useful in guiding revision of the disinfection program in such cases.

Critical equipment surfaces that come in contact with sterile drug products, containers, and closures must be sterilized at appropriate intervals (see § 211.67); disinfection alone is not sufficient (see section E below). Single-use disposable equipment and supplies that are purchased presterilized and depyrogenated and are discarded after one use need not be resterilized.

D. Environmental and Personnel Monitoring

The frequency and methods of environmental and personnel control and monitoring should be commensurate with the risk to product quality. For example, for non-sterile drugs, aqueous-based drugs present the highest microbiological risk to patients. Consequently, water system and environmental monitoring for aqueous non-sterile drug production should be performed more frequently than for non-aqueous non-sterile drugs. During aqueous non-sterile drug production, temperature and humidity should be monitored daily and air (viable[19] and nonviable particles) and surfaces (viable particles) should be monitored periodically (e.g., at least quarterly). Aseptic sterile drug production environments should be monitored at least daily during production. Also, monitoring of product residue may be necessary to ensure that the cleaning program is effective or containment is maintained, with an increased frequency of monitoring and sensitivity of methods when contamination poses a higher risk, such as when producing cytotoxic or highly sensitizing materials.

Additional Considerations for Sterile Drug Products

21 CFR 211.42(c)(10)(iv) requires establishing a system for monitoring environmental conditions in aseptic processing areas, and §§ 211.113(b) and 211.28(a) require personnel sanitation practices and gowning to be both acceptable and qualified for the operations they perform. For example, gowning procedures should ensure that there is no exposed skin on personnel involved in any production activities in, or that can directly affect, the ISO 5 area.[20] Procedures for monitoring the environment and personnel for the presence of viable particles and nonviable particles should be established and followed as described here.

Operations and appropriate written procedures designed to prevent microbial contamination include a well-defined and documented program for environmental monitoring that evaluates the potential routes of microbial contamination of the human drug that could arise from the air, surfaces, process, operation, and personnel practices (see §§ 211.42(c)(10)(iv), 211.100, 211.113(b)). The program should contain an appropriate detection component(s) to verify state of control of the environment. However, environmental monitoring equipment should not interfere with aseptic operations (e.g., instruments should not interfere with validated and appropriate airflow patterns). In particular, the program should:

- Cover all production shifts and include monitoring during normal production conditions.
- Include at least daily monitoring of the ISO 5 zone during operations.

[19] A *viable particle* consists of, or supports, one or more live microorganisms (see ISO 14644-6:2007, Cleanrooms and associated controlled environments—Part 6: Vocabulary).

[20] See guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* for further recommendations regarding gowning.

- Establish alert and action limits and appropriate responses when excursions occur.

- Describe the use of sampling (e.g., contact plates, swabs, active air samplers), alert and action limits and responses, and testing methods (e.g., media, plate exposure times, incubation times and temperatures) that are designed to detect environmental contaminants, including changes in microflora type and amount, and the scientific justification for the testing methods selected.

- Be supported by a scientific justification for sampling locations, based on risk, and sampling methods, which may be based on risk and peer-reviewed literature.

- Investigate results that exceed established limits or demonstrate adverse trends; determine product impact; and execute appropriate actions.

Personnel monitoring should:

- Include a routine program for daily/shift monitoring of operators' gloves and an appropriate schedule for monitoring other critical sites of the gown (e.g., gown sleeves for hood work) during or immediately after completion of aseptic operations. Monitoring should take place before planned disinfection so that actual operating conditions are being assessed.

- Establish and justify limits that are based on the criticality of the operation relative to the contamination risk to the product.

- Call for an investigation of results that exceed the established levels or demonstrate an adverse trend, a determination of the impact on the sterility assurance of finished products intended to be sterile, and the development and execution of appropriate corrective actions.

If microbiological media used in performing tests, including environmental and personnel monitoring, are not purchased from a qualified supplier,[21] the outsourcing facility or contract laboratory's procedures should establish the validity of each medium, including its growth potential. The quality control unit of an outsourcing facility that opts to rely on a contract laboratory for any of the duties described in this section of the guidance must ensure the

[21] A supplier could be qualified by following the recommendations for component supplier qualification in section III.G.1. of this guidance. Specifically, the outsourcing facility should have a quality agreement with each supplier and make the quality agreement available for review upon request by FDA. Each quality agreement should include, at a minimum: a description of the testing performed before a lot is released and shipped to the outsourcing facility and the specific quantitative (or qualitative, if applicable) results of a representative lot that would be provided on each COA; examples of testing records (such as growth promotion) that the supplier generates in performing release testing before shipping each lot to the outsourcing facility; a description of packaging, labeling, tamper-evident seals, and other features used to ensure package integrity while the purchased media is in distribution; and a commitment that the supplier will notify the outsourcing facility if there is identification of a problem with the quality of the media already shipped to the outsourcing facility.

existence, appropriateness, and implementation of contract laboratory procedures (see §§ 200.10, 211.22, 211.160).

E. Equipment

Several provisions of part 211 address controls over the equipment used to compound (see §§ 211.63, 211.65, 211.67, 211.68).

Equipment (mechanical, electronic, or automated) must be qualified as capable of performing its intended functions or operations before first use, and procedures for routine calibration and maintenance must be established and followed (see § 211.68). Equipment surfaces that come in contact with components, in-process materials, or drugs must not be reactive, additive, or absorptive so as to alter the quality of the drug (see § 211.65). Equipment needs to be designed and located to facilitate operations, cleaning, and maintenance, and equipment may require sanitization or sterilization to prevent contamination (see §§ 211.63, 211.67).

Outsourcing facilities may choose to use single-use disposable equipment (e.g., transfer tubing and temporary holding vessels), which reduces the need for cleaning between different batches and the potential for contamination (see § 211.67). Single-use disposable equipment should be inspected for damage or contamination following use. The suitability of single-use disposable equipment for its use in processing may be determined by the use of a valid COA from the supplier in lieu of testing or examination by the outsourcing facility (see §§ 211.65, 211.113). In addition, the integrity of the packaging of the single-use disposable equipment should be verified upon receipt before use.

Additional Considerations for Sterile Drug Products

Equipment that comes into contact with the drug product must be evaluated to ensure adequacy for intended use, including to ensure sterility and cleanliness at time of use (see §§ 211.65, 211.67(a)). For sterility and endotoxin limits, a valid COA may be used in lieu of testing by the outsourcing facility for single-use disposable equipment (see §§ 211.65, 211.113).

If the outsourcing facility does not use presterilized and depyrogenated single-use disposable equipment (e.g., filters, transfer tubing, temporary holding vessels), the equipment must be sterilized and depyrogenated before use through processes that have been validated[22] (see §§ 211.65, 211.67(a) and (b), 211.100, 211.113).

F. Containers and Closures

Controls for the containers and closures in which the compounded drug product is packaged are critical to ensuring the quality of compounded drug products and are expected to be implemented by outsourcing facilities (see §§ 211.80, 211.82, 211.84, 211.87, 211.94, 211.113).

[22] A process has been validated if it has been demonstrated and documented to consistently achieve the desired result when performed under defined conditions.

Scientifically sound and appropriate criteria[23] for containers and closures must be established to ensure that drug product containers and closures used for compounded drug products are suitable for each particular drug product for which they will be used (see § 211.160(b)). As part of the selection process, testing of the drug product container-closure system under the proposed storage conditions for the finished product must be performed to verify its ability to meet established quality specifications of the finished drug product over the expiry period (see §§ 211.94, 211.166). Testing must be performed again if the manufacturer's specification of the container or closure is changed (see §§ 211.94, 211.166). Appropriate procedures must be established for testing or verifying the testing, as applicable, of the containers and closures before use to determine whether they meet the criteria for use; the tests and results must be documented (see §§ 211.84(d)(3), 211.184). Each lot of containers and closures must be examined to verify identity and tested to ensure conformity with appropriate specifications before use (see § 211.84(d)).

Containers and closures must be handled and stored to protect them from risk of contamination and must be examined and cleaned to prevent introduction of contamination (see §§ 211.80, 211.82, 211.84, 211.94).

If containers or closures are stored for long periods in the absence of a supplier's expiration date or established in-use period, or if they are exposed to air, heat, or other conditions that might adversely affect the drug product container or closure, the containers and closures must be retested or re-examined for integrity and fitness for use before they are used (see § 211.87).

Additional Considerations for Sterile Drug Products

Containers and closures that come into contact with the drug product must be evaluated to ensure adequacy for intended use, including to ensure sterility and cleanliness at time of use (see §§ 211.80, 211.84(d)(6)).

FDA generally does not intend to take regulatory action against an outsourcing facility regarding the identification or testing of each lot of containers and closures if (1) for a finished drug product intended to be sterile, the supplier certifies and labels the material as ready-to-use, sterile, and nonpyrogenic; (2) the supplier's packaging integrity is verified upon receipt before use; and (3) the valid COA provided by the supplier is reviewed to verify that the product is represented to meet the required specifications established by the outsourcing facility, including sterility and depyrogenation. Any container or closure not meeting acceptance requirements must be rejected or not used until rendered suitable for use (see §§ 211.84(d) and (e)).

If the outsourcing facility does not use presterilized and depyrogenated containers and closures (e.g., vials, syringes), the containers and closures must be sterilized and depyrogenated before first use through processes that have been validated (see § 211.94(c)).

[23] For sterile drug products, see guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* for recommended test methods and criteria.

Procedures for storage, if appropriate, of sterilized containers or closures must be established in a manner to prevent contamination and to maintain sterility (see §§ 211.80(a) and (b)). For example, safeguards must be in place to ensure that containers and closures are not contaminated when held for use in areas where other materials are received, unpacked, and stored.

Containers or closures that are purchased as sterile must not be used after the supplier's expiration date without testing or examination to verify that container or closure integrity has been maintained (see § 211.87). Once the presterilized primary package has been breached, it should remain under the hood or in the ISO 5 area until the containers or closures are used. Where appropriate, any containers or closures removed from the ISO 5 area may be used for sterile production after resterilization using a validated process (which must also establish that the integrity of the container or closure is maintained) or used for drug products that do not require a sterilized container or closure (§§ 211.84, 211.87, 211.94).

G. Components

Controls over the source and quality of components are required (§§ 211.82, 211.84, 211.87, 211.113). When producing sterile drug products, one aspect of such controls is the consideration of whether the incoming components are non-sterile. The following controls are considered critical to ensuring the quality of compounded drug products and are expected to be implemented by outsourcing facilities.

Scientifically sound and appropriate specifications must be established for the components used in each drug product (see § 211.160(b)). Scientifically sound and appropriate specifications include those that address the attributes necessary to ensure the quality of the finished drug product and are appropriate for the intended use of the drug product, including the route of administration, as specified in the directions for use. A specification should generally conform to the model described in the ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*. A specification should minimally include those tests described in ICH Q6A's section 3.2, "Universal Tests/Criteria." Other dosage form-specific attributes may also be considered (see ICH Q6A section 3.3, "Specific Tests/Criteria"). Attributes can include identity, strength, purity, particle size, sterility, bacterial endotoxin level, content uniformity, microbial enumeration, tests for specified microorganisms, or other characteristics that could affect the quality of the final drug product.

To be eligible for the exemptions provided in section 503B of the FD&C Act, each bulk drug substance used in compounding must be "accompanied by a valid certificate of analysis" (section 503B(a)(2)(D)). FDA interprets this provision to mean that *each lot* of a bulk drug substance is accompanied by a valid COA.[24] FDA recommends that the COA conform to the model described in ICH Q6A.[25] In addition, to be eligible for the exemptions provided in section 503B of the

[24] Under certain conditions, a valid COA may be relied upon to minimize testing of incoming components (see § 211.84).

[25] The COA should be in English or should be translated into English to facilitate use by the outsourcing facility and review by FDA on inspection if needed.

FD&C Act, the bulk drug substance must be manufactured by an establishment that is registered under section 510 of the FD&C Act (section 503B(a)(2)(C) of the FD&C Act).

Each shipment of each lot of components must be tested to verify identity and evaluated for conformity with appropriate specifications before use (see § 211.84). Components should not be used beyond the supplier's labeled expiration (or re-test) date. If the component does not have an expiration date, the supplier should provide the date or testing should be conducted to establish an expiration date.

Components that are not approved finished drug products (both active pharmaceutical ingredients (APIs) and inactive ingredients) must be tested to verify identity and evaluated for conformity with appropriate specifications and, if necessary and depending on intended use, tested for endotoxin level and bioburden before use in compounding (see § 211.84). As described in § 211.84(d)(2), in lieu of testing each shipment of each ingredient, a supplier's COA can be accepted and evaluated to determine whether the lot can be used, provided that the following conditions are met (see also Figure 1 below):

- The reliability of the supplier's analyses has been established at appropriate intervals and through appropriate steps to:
  - Confirm the supplier's test results for those tests relevant to the specifications established for the compounded drug product.
  - Confirm that the ingredient meets the applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if one exists.[26]

  Such steps may include, but are not limited to, confirmatory testing and remote audit of the supplier's procedures.

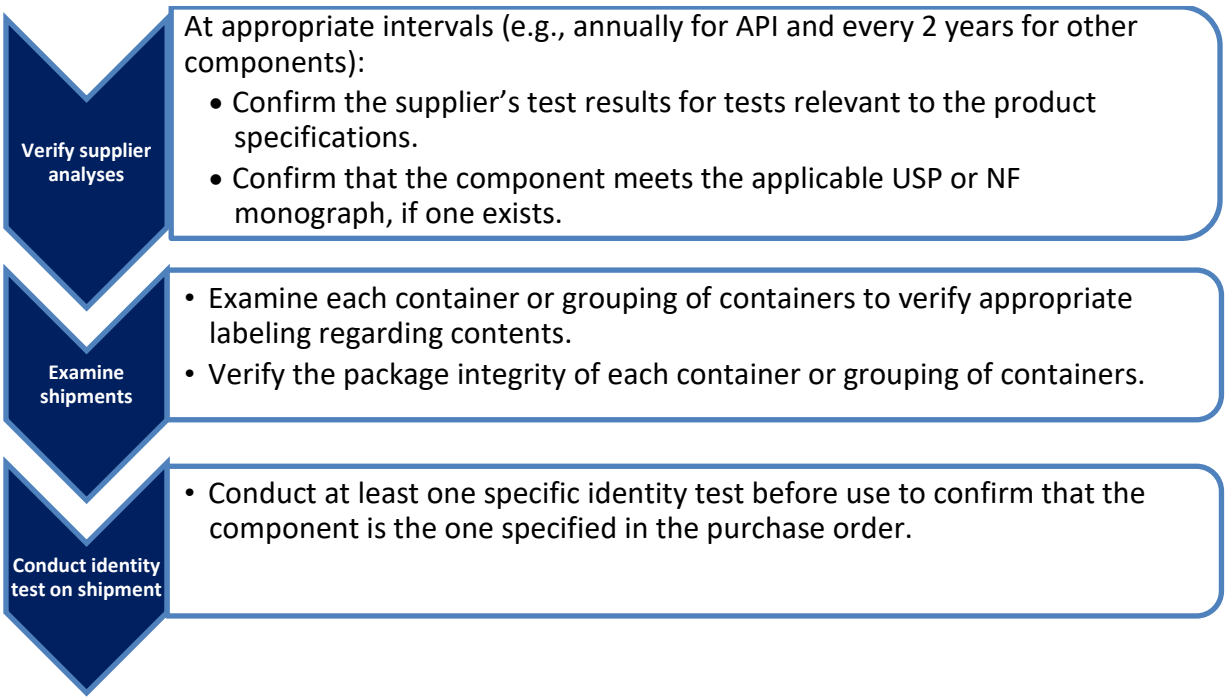
  FDA recommends that these steps be carried out no less frequently than annually for APIs and every 2 years for other components.
- At least one specific identity test has been conducted before use to confirm that the component is the one specified in the purchase order.

In addition, as required by § 211.82(a):

- Each container or grouping of containers of components must be examined to verify appropriate labeling regarding contents.
- The shipment's package integrity must be verified upon receipt before use.

[26] Components, both bulk drug substances and other ingredients, used in compounding must comply with the standards of the applicable USP or NF monograph, if such monograph exists, to qualify for the exemptions provided in section 503B of the FD&C Act (see sections 503B(a)(2)(B) and (a)(3)).

Figure 1. Using a Supplier's COA in Lieu of Testing*



* See §§ 211.84(d)(2) and 211.82(a).

Acceptance of incoming lots of non-sterile components (including water) for use in sterile drug products must include microbial and endotoxin testing and meet limits appropriate for the drug product's intended use (see § 211.84(d)(6)). FDA generally does not intend to take regulatory action against an outsourcing facility regarding the absence of such testing for water if it is purchased and certified as sterile and nonpyrogenic and if it is accompanied by a valid COA; however, the type of water purchased must be appropriate for its intended use (e.g., Sterile Water for Injection, USP) (§ 211.84). The quality of water produced on-site and used as an ingredient or processing aid must be tested regularly, using validated methods, at point of use to verify acceptable microbial quality, chemical quality, and endotoxin limits (§§ 211.84, 211.160). Acceptance criteria should be in agreement with those specified in the respective USP monograph and be appropriate for the intended use of the product.

Any component not meeting acceptance requirements must be rejected (see § 211.84(e)).

Components must be retested or re-examined for identity, strength, quality, and purity after storage for long periods or after exposure to air, heat, or other conditions that might adversely affect the component (see § 211.87). However, additional testing is unnecessary if each lot of components is stored under the supplier's labeled storage conditions, used within the established (i.e., as labeled, as provided by the supplier, or as determined by the outsourcing facility) retest or expiration date, and protected from contamination when portions of the lot are removed (see § 211.187).

1. Regulatory Policy Regarding Component Supplier Qualification Testing

FDA generally does not intend to take regulatory action against an outsourcing facility regarding additional testing to confirm the supplier's COA under § 211.84(d)(2) if the outsourcing facility enters into a quality agreement with each supplier of each component, makes the quality agreement available for review upon request by FDA, and each quality agreement includes, at a minimum:

- A description of the testing performed before a component lot is released and shipped to the outsourcing facility and the specific quantitative (or qualitative, if applicable) results of a representative lot that would be provided on each COA.

- Examples of testing records, such as chromatograms and spectrograms, that the component supplier generates in performing release testing before shipping each lot of the component to the outsourcing facility.

- A description of packaging, labeling, tamper-evident seals, and other features used to ensure package integrity while the purchased component is in distribution.

- A commitment that the component supplier will notify the outsourcing facility if any testing performed to generate the release COA is significantly modified (e.g., change in principle of operation for a test method).

- A commitment that the component supplier will notify the outsourcing facility under specified circumstances, including but not limited to a change in specifications or identification of a problem with the quality of a component already shipped to the outsourcing facility.

- A commitment that the supplier, if not the original component manufacturer, ensures the component's pedigree to the outsourcing facility, including:

    - A description of the supplier's qualification and audit requirements for each manufacturer from which the supplier purchases components.

    - A description of the supply chain authentication controls that the supplier has implemented to verify that before receipt, each component is transported through known and pre-established channels.

2. Regulatory Policy Regarding Testing for Finished Product To Be Used as a Source Material for Processing

FDA generally does not intend to take regulatory action against an outsourcing facility regarding the identification or testing of each lot of a product under § 211.84 that is to be used as a source

material and is an approved human finished drug product if all of the following conditions are met:

- The product was purchased directly from a manufacturer registered and listed with FDA under section 510 of the FD&C Act and has not been repacked or otherwise altered since initial manufacture, or the product was purchased from a distributor that certifies that it has not been repacked or otherwise altered since initial manufacture.

- The label of each lot of the product has been examined to verify that the product meets required specifications before use.

- No portion of the lot has been subject to a recall for reasons that would make it unsuitable for use.

- The shipment's package integrity has been verified upon receipt before use.

H. Production and Process Controls

Production and process controls are required when producing any drug product (see, e.g., §§ 211.22, 211.25, 211.28, 211.100, 211.111, 211.113, 211.188, 211.192).

Written procedures for production and process controls must be designed and followed to ensure the consistent production of a drug that meets the applicable standards of identity, strength, quality, and purity (see § 211.100). These controls are intended to ensure consistent yields; batches failing to meet the theoretical yield must be investigated (see §§ 211.186, 211.192). The degree of batch-by-batch control over product attributes or process parameters should be commensurate with the risk of those attributes and parameters to the process and product. These procedures should ensure documentation that all key process parameters are controlled and that any deviations from the procedures are justified.

Before use in production, equipment, components, containers, and closures should be visually examined for indications of damage, degradation, or contamination.

Batch records must provide complete documentation of the production of each batch of a drug product (see § 211.188).[27] The actual batch output (yield) must be compared to the projected (calculated) output for each drug product (see § 211.103). 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 (§ 211.192). 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 (see §§ 211.165, 211.192).

[27] For aseptic operations that occur in a hood, a contemporaneous recording to the batch record is one that occurs as soon as possible after completion of that unit operation.

Additional Considerations for Sterile Drug Products

1. General Production and Process Controls

If a drug product intended to be sterile is not terminally sterilized, there must be a validated sterilization step such as sterile filtration (see § 211.113(b)), and it is critical that the sterilization step occur as close to filling into the final product container as is feasible.

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 (see §§ 211.110(c), 211.111). 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 (see §§ 211.111, 211.113(b), 211.160). 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 (see §§ 211.65, 211.113(b)).

2. Drug Product Sterilization

a. 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.[28] 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, presterilization bioburden limits should be established (i.e., determining the number of microorganisms that can be reliably killed) and measured before sterilization. The selected sterilization method should both sterilize and maintain the strength, purity, quality, and package integrity of the sterile product.[29]

b. 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

[28] See guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.* For products such as pellets or powders, validation studies should be conducted using a biological indicator placed inside the product (i.e., inside the powder or pellets in their marketed containers) and spaced throughout the load to verify that the sterilization cycle results in sterility of the entire batch. Pellets should be placed in a defined and specified pattern in the sterilization chamber to demonstrate that appropriate lethality is delivered to each unit of the batch. Refer to ISO 11137-1:2006, Sterilization of health care products—Radiation—Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices; and ISO 11137-2:2013, Sterilization of health care products— Radiation—Part 2: Establishing the sterilization dose. See PDA Technical Report No.1 (Parenteral Drug Association 2007).

[29] See also USP General Chapters <1211> *Sterility Assurance* and <1229> *Sterilization of Compendial Articles.*

product cannot be filtered (e.g., certain suspensions), components should be sterilized (e.g., filter) at the last possible step (e.g., before forming the suspension). Manipulations following the component sterilization step must use aseptic practices to maintain sterility (see § 211.113).

Introductory training on microbiology, aseptic technique, cleanroom behavior, gowning, and procedures covering aseptic manufacturing area operations must be established and conducted before an individual is permitted to enter the aseptic manufacturing area or conduct operations in a laminar flow hood (see § 211.25(a)). Once introductory training outside of the aseptic manufacturing area is completed, further training based on department-specific requirements and individual job descriptions should be conducted. Individuals would be considered qualified to conduct aseptic operations after passing at least three successful, successive media fill simulations based on a scientifically sound protocol designed to verify the adequacy of their technique and behavior. Production simulations should be conducted in the same area where production occurs.

Techniques intended to maintain sterility of items and surfaces should include the following:

- Sterile materials should be handled only with sterile instruments.
- After initial gowning, sterile gloves should be regularly sanitized (e.g., using sterile 70 percent isopropyl alcohol) during production or, when needed, changed.
- Sterile and non-shedding gowning components should be used. Gowning components should be stored such that their sterility is not compromised.
- Torn or defective gowns should be changed immediately.
- Sterile products, the product-contacting surfaces of containers or closures, or other critical surfaces should not directly touch any part of the gown or gloves.
- Personnel should move slowly and deliberately within the cleanroom or hood.
- Personnel should keep their bodies and objects out of the path of unidirectional flow above open containers and products being filled.

Procedures for aseptic processing should address the following considerations:

- The design of equipment used in aseptic processing should limit the number and complexity of aseptic manipulations and should be suitable for its intended use.
- Personnel, material, and process flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, containers or closures, or the surrounding environment.
- In-process material, including intermediates such as stock solutions, should be placed in containers or closures that protect the material from the cleanroom environment.

Containers or closures holding sterile in-process material should not be breached in an environment less than ISO 5.

- Products should be transferred under appropriate cleanroom conditions. For example, transfer, loading, and unloading of aseptically filled product to and from the lyophilizer should occur only in classified areas that provide ISO 5 or better protection to the partially sealed containers.

- 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.

- Appropriate steps to prepare equipment for sterilization should be established, such as cleaning and use of wrapping that ensures protection while still allowing penetration of the sterilizing agent.

- The validation of sterilization operations for equipment associated with aseptic processing (e.g., holding vessels, filling equipment, lyophilizer) and periodic verification activities and results must be documented (see § 211.113(b)).

- For sterile drug products that are filter-sterilized, prefiltration bioburden limits should be established and measured before sterile filtration, unless all components consist of FDA-approved sterile drug products and/or components purchased and certified to be sterile and nonpyrogenic. A sterile pharmaceutical sterilizing-grade filter appropriate for the drug product (e.g., chemically compatible) should be used. The filter must be compliant with § 211.72 and filter integrity testing should be conducted after each filtration or production run.

For aseptic processing of sterile drug products (i.e., not subjected to terminal sterilization), the process for ensuring sterility must be validated (§ 211.113(b)), for example by conducting media fills simulating the production process. Validation should be performed semi-annually. Media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that are challenging to aseptic operations. The media fill program should address applicable issues such as the following:

- 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).

- 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.[30])

[30] When the possibility of contamination is higher based on the process design (e.g., manually intensive filling lines), a larger number of units, generally at or approaching the full production batch size, should be used. In contrast, a process conducted in an isolator can have a low risk of contamination because of the lack of direct human intervention and can be simulated with a lower number of units as a proportion of the overall operation.

- Lyophilization, when applicable.
- Aseptic assembly of equipment (e.g., at start-up, during processing).
- Number of personnel and their activities. (The maximum expected number of personnel should be included to simulate worst-case conditions.)
- Representative number of aseptic additions (e.g., filling containers and closures as well as sterile ingredients) or transfers.
- Shift changes, breaks, and gown changes (when applicable).
- Type of aseptic equipment disconnections/connections.
- Aseptic sample collections.
- Operational configurations in the ISO 5 zone and line speeds (when applicable).
- Weight checks.
- Container-closure systems (e.g., size, type, compatibility with equipment).
- Specific provisions in written procedures related to aseptic processing (e.g., conditions beyond which discarding of exposed materials in the ISO 5 area or line clearance is mandated).

I. Release Testing

Sections 211.165 and 211.167 require that finished drug products be tested to determine whether they meet final product specifications before their release for distribution. Section 211.22 establishes that the quality control unit is responsible for ensuring that the finished drug product is not released until this testing is conducted and the results confirm that the finished drug product meets specifications. Procedures for final release testing should be established and followed as outlined here.

Appropriate specifications must be established for each drug product (see § 211.160(b)). Specifications must address those attributes necessary to ensure the quality of the finished drug product and must include, at a minimum (§§ 211.160(b), 211.165, 211.167):

- Identity and strength of the API.[31]

[31] If the API is known (from literature or other scientific information) to have the potential to form genotoxic degradants as discussed in ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk*, the presence of the impurity or impurities should be evaluated as part of the assay or, if the assay method is not sufficiently sensitive, using a different test.

- Purity of the drug product.

- For drug products purporting to be sterile and/or nonpyrogenic, sterility[32] and a limit for bacterial endotoxins.

- Antimicrobial effectiveness for sterile drug products labeled as multiple dose and for aqueous non-sterile drug products labeled as multiple dose.[33] If antimicrobial effectiveness testing was previously performed using the subject formulation and container-closure system, preservative content testing may be used in lieu of a full antimicrobial effectiveness study. Appropriate specifications for aqueous drug products labeled as multiple dose include assurances that the product is adequately self-preserving or contains appropriate preservative content to limit microbial proliferation of microorganisms and assure that the product maintains its quality and purity for each dose.[34]

The product must also meet any other specifications included in an applicable USP monograph (see, e.g., section 501(b) of the FD&C Act). In addition, FDA recommends consideration of the following specifications:

- Color, clarity.

- pH, if applicable (e.g., for aqueous formulations).

- For drug products that are not solutions, content uniformity.[35]

- For drug products that are non-sterile, microbial testing (i.e., microbial enumeration, tests for specified microorganisms).

[32] Sterility testing should be conducted using USP General Chapter <71> *Sterility Tests*. Any other method used for sterility testing should be validated. See, for example, USP General Chapter <1223> *Validation of Alternative Microbiological Methods* or PDA Technical Report No. 33 (see Parenteral Drug Association 2013) for recommended validation methods.

[33] See USP General Chapter <51> *Antimicrobial Effectiveness Testing* for more information.

[34] Unsafe injection practices, including the improper use of needles, syringes, and vials for more than one patient, threaten patient safety and have resulted in multiple blood borne bacterial and viral infection outbreaks. Bacterial infections have been transmitted to patients when single-dose containers were used improperly, the contents became contaminated, and these contents were then administered to multiple patients. Therefore it is critical that drug products that are not adequately self-preserving and do not contain appropriate preservative content be labeled as single-dose to prevent such risks to health.

[35] For oral solid dosage forms (e.g., tablets and capsules), content should be assessed between dosage units. For nonsolid oral products (e.g., suspensions), the content should be assessed within the container (e.g., from the top and bottom of the container).

- For drug products that are solutions purporting to be sterile, a limit for visible particles[36] and subvisible particles (10µm-100µm).[37]

Other appropriate specifications for generally recognized attributes for the dosage form, such as those described in ICH Q6A, should also be considered. For example, the specification for immediate release solid oral dosage forms typically includes disintegration testing, while non-immediate release dosage forms include dissolution testing as a measure of the release rate of drug substance from the drug product (see § 211.167).

Procedures for release must be established that ensure that each batch of a drug product is not released until the following have been completed (see §§ 211.22, 211.165, 211.167, 211.192):

- An appropriate laboratory determination has been conducted to ensure that each batch of a drug product conforms to specifications.

- A review of environmental and personnel monitoring data, if applicable, has been conducted to ensure that manufacturing conditions were acceptable during production of the batch.

- Associated laboratory data and documentation have been reviewed by the quality control unit, and they demonstrate that the drug product meets specifications.

- A designated qualified individual from the quality control unit has authorized final release.

Under certain conditions described in Appendix A, FDA generally does not intend to take action against an outsourcing facility regarding the release testing requirements described immediately above and in the appendix.

Additional Considerations for Sterile Drug Products

Finished product sterility testing provides additional verification of sterility, even for those products compounded from sterile starting materials, because an unexpected event posing a risk to sterility may have occurred but may not have been detected. Appendix A describes the conditions under which FDA generally does not intend to take regulatory action against an outsourcing facility regarding finished product sterility testing based on mitigating factors, such as the use of a validated terminal sterilization method and the use of other approaches to evaluate sterility of the finished product before release.

[36] Such a limit may be established for any solution by following USP General Chapter <790> *Visible Particulates in Injections.*

[37] Applicable only to parenteral preparations. See USP General Chapters <788> *Particulate Matter in Injections* and <789> *Particulate Matter in Ophthalmic Solutions* for additional information.

For finished products purporting to be nonpyrogenic, the product must meet endotoxin limits[38] before release (§ 211.167). For finished products compounded from starting materials that are sterile and nonpyrogenic, endotoxin testing can be conducted on all starting materials (through testing of the starting materials, or reliance on a statement of the limit met on a valid COA, or where specified in an applicable USP monograph) or through testing of samples of the finished product. The fact that a starting material is labeled nonpyrogenic does not necessarily ensure that the finished product will meet the appropriate endotoxin limit because starting materials, including FDA-approved products, may have been tested against different endotoxin limits, depending on the intended dose and the route of administration.[39]

J. Laboratory Controls

When testing components, in-process materials, and finished drug products, laboratories must use controls to ensure the reliability of the tests (§ 211.160). Each laboratory used to test components, in-process materials, or finished drug products—whether in-house or external to the outsourcing facility—must employ the following critical aspects of laboratory controls to ensure the quality of non-sterile and sterile drug products compounded by the outsourcing facility (see §§ 211.160, 211.194):

- Follow appropriate written procedures for the conduct of each test and document the results.
- Design sampling and testing procedures to ensure that components, in-process materials, and drug products conform to the specifications set for the drug product.
- Use analytical methods and equipment that are suitable for their intended use and are capable of producing valid results. 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.
- Keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays.

When an outsourcing facility seeks the services of a contract facility to perform all or part of the testing of a drug, the outsourcing facility's quality control unit is responsible for approving and rejecting drugs tested by the contractor. See §§ 200.10(b) and 211.22(a) and guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*. In addition, FDA recommends that contract facilities performing testing of a drug be ISO 17025 accredited.

[38] Typically, endotoxin testing is not required for topically administered ophthalmic products. See USP General Chapter <771> *Ophthalmic Products—Quality Tests.*

[39] See also guidance for industry *Pyrogens and Endotoxins Testing: Questions and Answers*.

K. Stability/Expiration Dating for Compounded Drug Products

1. Stability Program and Beyond-Use Dating

A stability program must be established to assess the stability characteristics of finished drug products, and the results of stability testing must be used to determine appropriate storage conditions and expiration dates (§ 211.166). Stability testing is used to ensure that a drug product will retain its quality (e.g., strength) and remain sterile, if applicable, through the labeled expiration date. A stability program for compounded drug products should use past experiences, available literature, and fundamental scientific principles to establish the parameters for the program. An expiration date is established through the conduct of a stability program that includes testing to assess the product's performance against specifications after aging to the desired expiration date (§ 211.137); the conditions outlined in ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* are recommended.

FDA understands that a compounded drug's batch size may be small and the frequency of batch production may vary considerably. The policies regarding stability testing and expiration dating in this guidance recognize these potential aspects of compounded drug production while addressing concerns regarding the quality of these products using a risk-based approach.

FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing requirements if all of the following apply:

- The drug product is compounded solely by combining two or more drug products approved under section 505 of the FD&C Act.
- The approved drug product labeling of at least one of the components specifies how to assign an *in-use time*.
- The compounded drug product has been prepared and labeled with an in-use time in accordance with the approved product labeling.
- The in-use time is used as the expiration date, provided the in-use time does not exceed the expiration date of any of the approved drug products used to compound the drug. If two or more approved drug products with in-use times are used in the compounded drug product, the shortest in-use time is used as the expiration date for the compounded drug product.

In addition, taking into account the unique aspects of compounding, FDA generally does not intend to take regulatory action against an outsourcing facility under the conditions described in the remainder of this section and in Appendix B, such as using a BUD established through limited stability testing or, for certain lower risk situations, using a default BUD as the expiration

date, in lieu of establishing an expiration date through the conduct of a full stability program required under part 211,[40] if all of the following apply:

- The compounded drug's BUD does not exceed appropriately established expiration or retest-by dates for any of the components used to compound the drug.

- If the drug is compounded from an approved drug product, and the approved product labeling recommends one type of storage (e.g., refrigeration through the expiry date, such as 18 months), but also provides for storage at another condition (e.g., stable at room temperature for a time frame shorter than the expiry date, such as up to 14 days), the compounded drug product is not labeled with a BUD that is longer than the relevant storage time frame in the approved product labeling (e.g., the BUD of the compounded drug does not exceed 14 days for room temperature).

In addition, for repackaged products, FDA generally does not intend to take regulatory action against an outsourcing facility under the conditions described in the remainder of this section and in Appendix B, in lieu of establishing an expiration date through the conduct of a full stability program, if (1) the BUD does not exceed the expiration date of the drug product that is being repackaged; and (2) if the approved product labeling for the drug product being repackaged recommends one type of storage (e.g., refrigeration through the expiry date, such as 18 months) but also provides for storage at another condition (e.g., stable at room temperature for a time frame shorter than the expiry date, such as up to 14 days), the repackaged product is not labeled with a BUD that is longer than the relevant storage time frame in the approved product labeling (e.g., the BUD does not exceed 14 days for room temperature). For more information on repackaging, see the guidance for industry *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*.

Whether you use an expiration date or BUD to be used as an expiration date according to the provisions outlined below and in Appendix B, the two studies below are required to be completed before a batch is released (see §§ 211.166, 211.167). Each study only needs to be conducted once for each formulation and container-closure system, and a bracketing or matrixing approach can be considered to minimize the amount of testing. See Appendix B for more information regarding bracketing approaches.

- **Container-closure integrity testing** is conducted on samples aged to or beyond the desired BUD or expiration date to ensure that sterility is maintained over that time period.[41]

[40] To meet the conditions under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

[41] See USP General Chapter <1207> *Package Integrity Evaluation—Sterile Products* for more information on container-closure integrity testing.

- **Antimicrobial effectiveness testing** for drug products labeled or intended to be multiple dose is conducted on samples aged to the proposed BUD or expiration date. (Note that antimicrobial effectiveness testing is container-closure specific.)[42]

Tables 2 and 3 highlight the conditions under which FDA generally does not intend to take regulatory action against an outsourcing facility for assigning a BUD to be used as an expiration date in lieu of conducting full stability studies required under part 211.

a. Non-sterile limited stability testing

For small batches (≤5,000 units[43] in an aggregate batch[44]), FDA generally does not intend to take regulatory action if the relevant default BUDs provided in Appendix B are used for the expiration date and the conditions set forth in Appendix B are met. Alternatively, for small batches, FDA generally does not intend to take regulatory action if limited stability testing is conducted to support a BUD longer than the relevant default BUDs in accordance with Appendix B, and that BUD is used as an expiration date in lieu of conducting full stability studies required under part 211. For larger batches (>5,000 units in an aggregate batch), FDA generally does not intend to take regulatory action regarding stability testing if the relevant conditions for the limited stability testing outlined in Appendix B are met. If, at any time during a 6-month reporting period, the total number of units compounded exceeds the 5,000-unit limit, the conditions applicable to small batches (i.e., ≤5,000 units) do not apply.

Table 2. BUDs for Non-Sterile Compounded Drug Products, by Aggregate Batch Size

Aggregate Batch Size (over 6-month reporting period)	Default BUD (no testing)	BUD Based on Limited Stability Testing
≤5,000 units	Default BUD, which may be further limited by literature or other scientific information. See Appendix B for the conditions that must be met.	Data-driven stability program. See Appendix B for the conditions that must be met.
>5,000 units	N/A. Default BUDs are not applicable to large aggregate batch sizes.	Data-driven stability program. See Appendix B for the conditions that must be met.

[42] See USP General Chapter <51> *Antimicrobial Effectiveness Testing* for more information.

[43] *Units* are individual tablets or capsules for solid oral dosage forms and suppositories, inserts, or immediate containers (e.g., vial, syringe, IV bag, tube) for other dosage forms.

[44] For the purposes of this guidance, batch size has been considered by defining *aggregate batch* as the sum of all units produced from any number of batches over the 6-month period for which a drug product report is submitted. For more information about product reports, see the guidance for industry *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

b. Sterile limited stability testing

For small batches (≤1,000 units in an aggregate batch), FDA generally does not intend to take regulatory action if the relevant default BUDs provided in Appendix B are used for the expiration date and the conditions set forth in Appendix B are met. Alternatively, for small batches, FDA generally does not intend to take regulatory action if limited stability testing is conducted to support a BUD longer than the relevant default BUDs in accordance with Appendix B, and that BUD is used as an expiration date in lieu of conducting full stability studies required under part 211. For larger batches (>1,000 units in an aggregate batch), FDA generally does not intend to take regulatory action regarding stability testing if the relevant conditions for the limited stability testing outlined in Appendix B are met. If, at any time during a 6-month reporting period, the total number of units compounded exceeds the 1,000-unit limit, the conditions applicable to small batches (i.e., ≤1,000 units) do not apply.

Table 3. BUDs for Sterile Compounded Drug Products, by Aggregate Batch Size

Aggregate Batch Size (over 6-month reporting period)	Default BUD (no testing)	BUD Based on Limited Stability Testing
≤1,000 units	Default BUD, which may be further limited by literature or other scientific information. See Appendix B for the conditions that must be met.	Data-driven stability program. See Appendix B for the conditions that must be met.
>1,000 units	N/A. Default BUDs are not applicable to large aggregate batch sizes.	Data-driven stability program. See Appendix B for the conditions that must be met.

2. Establishing an In-Use Time for Sterile Drug Products

To be eligible for the exemptions under section 503B of the FD&C Act, the container for the compounded drug product must include directions for use, including, as appropriate, dosage and administration (section 503B(a)(10)(B) of the FD&C Act). If the compounded drug product requires additional manipulation before administration (e.g., reconstitution and/or dilution), FDA interprets the directions for use requirement to include an in-use time because the health care practitioner who manipulates or administers the drug would need to know how long it is expected to retain its quality after being manipulated. Furthermore, stability studies (as required by § 211.166) would be needed to support the stated in-use time. However, FDA generally does not intend to take regulatory action regarding the requirement to have data to support the stated in-use time, such as microbial challenge and stability studies, if the sterile product has directions for use that include an in-use time less than 4 hours at room temperature or less than 24 hours refrigerated.[45]

[45] For a description of methods and acceptance criteria for microbial challenge studies, see Metcalfe 2009.

Under §§ 211.160 and 211.165(b), appropriate laboratory testing of products required to be free of objectionable microorganisms are required, and laboratory controls must include scientifically sound and appropriate specifications and test procedures designed to provide assurance that the product conforms to appropriate standards of identity, strength, quality, and purity. For multiple dose products, appropriate laboratory tests and specifications include ones for antimicrobial effectiveness, whether the product contains a preservative or antimicrobial activity is inherent in the formulation. See USP General Chapter <51> for antimicrobial effectiveness test methods and acceptance criteria. If the acceptance criteria described in USP General Chapter <51> are met, labeling up to a 28-day in-use period is considered to be appropriate for multiple-dose products, subject to the conditions regarding stability testing discussed below.

In addition to microbial challenge studies, the stability of the manipulated product must be assessed (see § 211.166). FDA generally does not intend to take regulatory action regarding the requirement to conduct full stability studies to assess the stability of the manipulated product if the tests conducted as part of the limited stability testing described in Appendix A are conducted on samples aged to at least 2/3 of the labeled BUD (if longer than the default BUDs outlined in Appendix B), manipulated (e.g., reconstituted or diluted) as described in labeling, and then held for the desired in-use time (up to 28 days).

The labeled directions for use[46] should include instructions to the health care provider or patient that the time in storage plus the administration phase should not exceed the BUD. Consider, for example, a sterile powder formulation in a vial that must be reconstituted with Sterile Water for Injection, USP, before patient administration with a label that includes an in-use-time of within 4 hours at room temperature or within 24 hours if refrigerated. The in-use time begins when the sterile powder vial is entered and reconstituted with Sterile Water for Injection, USP. The reconstituted solution should be administered to the patient within 4 hours if the solution is held at room temperature or within 24 hours if it is stored in the refrigerator.

3. In-Use Time and BUDs for Sterile Drug Products

The outsourcing facility should establish the BUD placed on a compounded drug product's label, taking into consideration that the BUD is the date/time after which the product is to be discarded. The labeled directions for use should include instructions to the health care provider or patient accordingly. If the product does not require any manipulation (e.g., dilution or reconstitution) before administration, the directions for use should advise that administration to the patient should be completed before reaching the BUD. For example, if an IV bag containing a compounded drug product with a BUD of 24 hours is to be infused to the patient over a period of 4 hours, the infusion should begin by 20 hours to ensure that administration will be complete before reaching the BUD, at which point the compounded drug product should be discarded.

[46] Section 503B(a)(10)(B) of the FD&C Act provides the following: "The container from which the individual units of the drug are removed for dispensing or for administration . . . shall include . . . directions for use, including, as appropriate, dosage and administration."

L. Packaging and Labels

Packaging of non-sterile and sterile drugs must be appropriate to the product and capable of ensuring the sterility, if applicable, and integrity of the product until it is administered to a patient (see §§ 211.94, 211.122). 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 (§§ 211.122, 211.125, 211.130, 211.134).

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) (§ 211.94).

- Adequate controls have been established for issuing labels, examining issued labels, and reconciliation of used labels to prevent mix-ups (§ 211.125).

- There is adequate separation between the labeling and packaging operations of different products, including ones with different strengths or containers or closures, to prevent mix-ups (§ 211.130).

- 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 of time (§ 211.130).

- Packaging records include results of examinations of labels used (§ 211.134) and specimens or copies of all labeling used (§ 211.188).

- The labeled finished drug product has been examined for accuracy before release (§ 211.134).

M. Reserve Samples

An appropriately identified reserve sample that is representative of each lot or batch of drug product must be retained and stored under conditions consistent with product labeling (§ 211.170). FDA generally does not intend to take regulatory action against an outsourcing facility regarding reserve sample requirements if all of the following apply:

- Once >10,000 units are produced of a given drug product formulation and container-closure system in a 6-month reporting period, an appropriately identified and representative reserve sample is collected each time 1,000 units of that specific formulation and container-closure system is produced for the remainder of the current reporting period and for the entire subsequent 6-month reporting period.

- The reserve sample is retained and stored under the labeled storage conditions and in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics (e.g., same material, same headspace for liquids).

- The reserve sample is held for at least 30 days following the expiration date.

- The reserve sample consists of at least the quantity of drug product necessary for all tests required at release, except for sterility and pyrogen testing.

N. Complaint Handling

Outsourcing facilities must have procedures for handling complaints that they receive about their compounded drug products (§ 211.198). Written and oral complaints concerning the quality or purity of a drug product must be reviewed by the quality control unit, which must determine the need to investigate the complaint in accordance with § 211.192 (§ 211.198). If an investigation is needed, in addition to the quality control unit, personnel appropriate to evaluate the complaint should be involved. Complaint handling procedures must include provisions for review to determine whether the complaint represents an adverse event that must be reported to FDA (see § 211.198, section 301(ccc)(3) of the FD&C Act, and the guidance for industry *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*).

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ISO 11137-1:2006, Sterilization of health care products—Radiation—Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices

ISO 11137-2:2013, Sterilization of health care products—Radiation—Part 2: Establishing the sterilization dose

ISO 14644-1:2015, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration

ISO 14644-6:2007, Cleanrooms and associated controlled environments—Part 6: Vocabulary

V. GLOSSARY

Action Limit: An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

Active Pharmaceutical Ingredient (API): Any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. *API* does not include intermediates used in the synthesis of the substance.

Aggregate Batch: The sum of all units produced from any number of batches over the 6-month period for which a drug product report is submitted.

Alert Limit: An established microbial or airborne particle level giving early warning of potential drift from normal operating conditions and triggering appropriate scrutiny and follow-up to address the potential problem. Alert limits are always lower than action limits.

Aseptic: Free from germs that cause disease; sterile.

Aseptic Manufacturing Area: The classified part of a facility that includes the aseptic processing room and ancillary cleanrooms.

Aseptic Process: The process by which a sterile product is packaged in a sterile container in a manner that maintains sterility.

Batch: A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single compounding order during the same cycle of production.

Beyond-Use Date (BUD): A date beyond which a compounded drug product should not be used. A BUD notifies the user of the period during which a compounded drug product's required quality characteristics (e.g., sterility, strength, purity, freedom from particulate matter) can be ensured.

Bioburden: The total number of microorganisms associated with a specific item before sterilization.

Biological Indicator (BI): A population of microorganisms inoculated onto a suitable medium (e.g., solution, container or closure) and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process. The challenge microorganism is selected based on its resistance to the given process. Incoming lot D-value and microbiological count define the quality of the BI.

Bulk Drug Substance: See definition for *active pharmaceutical ingredient*.

Cleanroom: A room designed, maintained, and controlled to prevent particle and microbiological contamination of drug products. Such a room is assigned a classification based on reproducibly meeting appropriate air cleanliness limits.

Component: Any ingredient intended for use in the manufacture of a drug product, including ingredients that may not appear in the final drug product.

Critical Area: An area designed to maintain sterility of sterile materials.

Critical Surface: Surfaces that may come into contact with or directly affect a sterilized product or its containers or closures.

Depyrogenation: A process used to destroy or remove pyrogens (e.g., endotoxins).

Disinfection: A process by which surface bioburden is reduced to a safe level or eliminated.

Endotoxin: A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall. Endotoxins can lead to reactions ranging from fever to death in patients receiving injections.

Expiration Date: A date on the drug product label that indicates how long the drug can meet applicable standards of identity, strength, quality, and purity under labeled storage conditions before it is used. Expiration dates are determined based on product-specific stability studies evaluating the specific formulation of a drug product, in the specific container in which it is to be stored, and under the conditions to which it may be exposed. Temperature, humidity, and light are some of the factors that can affect whether and how much a drug product degrades over time.

HEPA Filter: A high-efficiency particulate air filter with minimum 0.3 μm particle retaining efficiency of 99.97 percent.

In-Use Time: The maximum amount of time that can be allowed to elapse between penetration of a container-closure system once the drug product has been sterilized, or after a lyophilized drug product has been reconstituted, and before patient administration.

Intervention: An aseptic manipulation or activity that occurs in the critical area.

Isolator: A decontaminated unit supplied with ISO 5 or higher air quality that provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding cleanroom air and personnel).[47]

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, a specific identified amount produced in a unit of time or quantity in a manner that provides assurance of its having uniform character and quality within specified limits.

Operator: Any individual participating in the aseptic processing operation, including line set-up, filler, or maintenance, or any other personnel associated with aseptic line activities.

Pyrogen: A substance that induces a febrile reaction in a patient.

Terminal Sterilization: The application of a lethal agent (e.g., heat) to sealed, finished drug products for the purpose of achieving a predetermined sterility assurance level (SAL) of usually less than 10^{-6} (i.e., a probability of a non-sterile unit of greater than one in a million).

Unidirectional Flow: An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

Viable Particle: A particle that consists of, or supports, one or more live microorganisms.

[47] See Appendix 1 in guidance for industry *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*.

APPENDIX A. CONDITIONS UNDER WHICH FDA GENERALLY DOES NOT INTEND TO TAKE REGULATORY ACTION REGARDING CERTAIN RELEASE TESTING REQUIREMENTS

Procedures for release must be established that ensure that each batch of a drug product is not released until the following have been completed (see §§ 211.22, 211.165, 211.167(a), 211.192):

- An appropriate laboratory determination has been conducted to ensure that each batch of a drug product conforms to specifications.
- A review of environmental and personnel monitoring data, if applicable, has been conducted to ensure that manufacturing conditions were acceptable during production of the batch.
- Associated laboratory data and documentation have been reviewed by the quality control unit, and they demonstrate that the drug product meets specifications.
- A designated qualified individual from the quality control unit has authorized final release.

A. Non-Sterile Drug Products

FDA generally does not intend to take regulatory action against an outsourcing facility regarding these release requirements **under the conditions described in Table A,** which is at the end of Appendix A. For any given product, consider which conditions in Table A apply. If multiple conditions apply, choosing the least stringent option for **each** individual batch release test among the applicable conditions would be consistent with the enforcement policy set forth in this appendix.

Example 1: All of the following conditions apply:

- The batch size is >60 units.
- The water activity is ≤0.6 (it is not a solid dosage form).
- The product is tested for strength by a method that is highly specific (e.g., high performance liquid chromatography (HPLC)) and uses a reference standard.

From Table A, conditions 2b and 3 apply; under those conditions, FDA generally does not intend to take regulatory action against an outsourcing facility regarding batch release tests for identity, AET/preservative content, microbial enumeration, or tests for specified microorganisms if the outsourcing facility assessed strength, content uniformity, pH, appearance, and the other appropriate specifications for that product.

Example 2: All of the following conditions apply:

- The batch size is 30 units *each month*.

- The starting material is a bulk drug substance.

- The product is a solid dosage form.

- The product is tested for strength by a method that is highly specific (e.g., HPLC) and uses a reference standard.

From Table A, conditions 1b and 3 apply for the first batch of 30 units; conditions 2c and 3 apply for the second batch of 30 units (i.e., when a total of 60 units has been produced); conditions 1b and 3 apply for the third batch of 30 units; and so on. Under those conditions, FDA generally does not intend to take regulatory action against an outsourcing facility regarding batch release testing for identity, content uniformity, pH, AET/preservative content, microbial enumeration, tests for specified microorganisms, or the other appropriate specifications if the outsourcing facility assessed strength and appearance for every batch and also assessed content uniformity and the other appropriate specifications for that product for every other batch.

B. Sterile Drug Products

FDA generally does not intend to take regulatory action against an outsourcing facility regarding these release requirements **as they apply to sterility testing** if sterility testing is *initiated before* batch release (see also Table D in Appendix B for BUDs for products released without a completed sterility test) and established procedures specify that if the drug product fails to meet a criterion for sterility:

- All facilities that received the drug product are notified immediately of the test results and provided with any appropriate information and recommendations to aid in the treatment of patients.

- The notification is documented.

- FDA is notified in writing within 5 working days.[48]

In addition, FDA generally does not intend to take regulatory action against an outsourcing facility regarding the release requirements for sterility testing **under the conditions described in Table B,** which is at the end of Appendix A. For any given product, consider which conditions in Table B apply. If multiple conditions apply, choosing the least stringent option for **each** individual batch release test among the applicable conditions would be consistent with the enforcement policy set forth in this appendix.

Example 1: All of the following conditions apply:

- The batch size is 30 units *each month*.

[48] Reports should be emailed to FDA at OFAlertReport@fda.hhs.gov.

- The product is a solution or total parenteral nutrition (TPN) and the bulk solution but not the finished drug product is tested for identity and strength immediately before filling into the final and prelabeled drug product containers.

- The product is terminally sterilized using a validated sterilization cycle that uses physical, chemical, or biological indicators.

From Table B, conditions 2, 5, and 6 apply to the first batch of 30 units; conditions 1, 5, and 6 apply to the second batch of 30 units (i.e., when a total of 60 units has been produced); and so on. Under those conditions, FDA generally does not intend to take regulatory action against an outsourcing facility regarding batch release testing for identity, strength, sterility, pH, visible particulates, subvisible particulates (where applicable), or other appropriate specifications, including USP monograph specifications, if the outsourcing facility conducted testing for endotoxin, color, and clarity on that product for each batch and also conducted testing on pH, visible particulates, subvisible particulates (where applicable), and other appropriate specifications, including USP monograph specifications on every other batch.

Example 2: Both of the following conditions apply:

- The batch size is >60 units.

- Drug product is a multicomponent injectable drug product (e.g., total parenteral nutrition product, cardioplegia solution) compounded from APIs produced only by FDA-registered manufacturers, the finished product is compounded using automated equipment with validated software, and the equipment is calibrated immediately before and after each personnel shift.

From Table B, conditions 1 and 5 apply; under those conditions, FDA generally does not intend to take regulatory action against an outsourcing facility regarding batch release testing for identity and strength if the outsourcing facility conducted testing for sterility, endotoxin, pH, color, clarity, visible particulates, subvisible particulates (where applicable), and other appropriate specifications, including USP monograph specifications.

C. Additional Considerations

FDA generally does not intend to take regulatory action against an outsourcing facility regarding the requirement to test the *finished* product before release (see § 211.165, 211.167) if the drug product is aseptically filled into secured, sterile cartridges or cassettes that are designed to prevent misuse through a locking mechanism that prevents the outsourcing facility from testing the finished product, and all testing/examinations are conducted on a sample from the container that holds the pooled, compounded drug product (e.g., pump reservoir) after all final containers are filled.[49]

[49] See Table 2 in USP General Chapter <71> *Sterility Tests* for more information regarding the volume to be sampled.

To reduce the need for the manufacturing of additional units to meet the sterility testing requirement (see § 211.167) by following the procedures in USP General Chapter <71> *Sterility Tests*, FDA generally does not intend to take action against an outsourcing facility regarding the number of units tested if:

- For batch sizes up to and including 10 units that do not also meet conditions 3 or 6 in Table B, at least 1 unit is tested; and

- For batch sizes of greater than 10 units and fewer than 40 units, the sterility test is conducted using a number of containers that equals 10 percent rounded up to the next whole number.

Table A. Conditions Regarding Batch Release Tests for Non-Sterile Drug Products

Conditions	Batch Release Test ○ Test for which FDA generally does **not** intend to take regulatory action under the conditions listed ● Test expected to be performed, if applicable								
	Identity	**Strength**	**Content Uniformity[c]**	**pH**	**Appearance**	**AET/Preservative Content[d]**	**Microbial Enumeration (bacteria and fungi)[e]**	**Tests for Specified Microorganisms[e]**	**Other Appropriate Specifications[f]**
Tests are conducted according to these conditions …									
1. Batch size <60 units,[a] if omitted tests are performed once 60 units are produced[b]									
1a. Starting from FDA-approved product	○	○	○	○	●	○	○	○	○
1b. Starting from bulk drug substance	●	●	○	○	●	○	○	○	○
2. Batch size ≥60 units *or* once 60 units are produced[b] and considering the following characterizations of water activity:									
2a. Water activity >0.6	●	●	●	●	●	●	●	●	●
2b. Water activity ≤0.6 (other than solid dosage forms)	●	●	●	●	●	○	○	○	●
2c. Solid dosage forms	●	●	●	○	●	○	○	○	●
… unless conditions 3 or 4 also apply. If so, choosing the least stringent option for each test among applicable conditions would be consistent with the enforcement policy set forth in this appendix.									
3. Product tested for strength by method that is highly specific (e.g., HPLC) and uses a reference standard	○	●	●	●	●	●	●	●	●
4. Compounded drug product is single dilution of FDA-approved drug product, or is made from one or more dilutions of FDA-approved drug product performed per labeling dilution instructions and using automated equipment calibrated immediately before and after production	○	○	●	●	●	●	●	●	●

[a] Individual tablets or capsules for solid oral dosage forms and suppositories, inserts, or containers (e.g., vial, syringe, IV bag, tube) for other dosage forms.

[b] Omitted tests under these conditions need only be performed one time after a single batch of 60 or more units has been produced or once 60 or more units have been produced in more than 1 batch within a year of the time the first batch is produced, and resets once testing has been performed or at 1 year from the time the first batch is produced if a minimum of 60 units was not produced. For example, if the batch size is consistently 30 units (e.g., tubes) of a particular volume of drug, the omitted tests are conducted on every second batch produced. Or, if the first, second, and third batches in the year include 25, 30, and 10 units respectively, the omitted tests are performed on the third batch because the minimum of 60 units has been met.

[c] FDA generally does not intend to take regulatory action if content uniformity testing is not performed on solutions.

[d] If the drug product is self-preserving, then either test for the API/excipient that is providing the preserving effect or conduct antimicrobial effectiveness testing (AET). For products with a preservative, conduct preservative content testing. Nonetheless, AET should be performed at least one time on a formulation using the lowest preservative concentration for the subject formulation and container-closure system.

[e] See, for example, USP General Chapter <1111>.

[f] These include generally recognized attributes for each dosage form such as those described in ICH Q6A or USP monographs or general chapters.

Table B. Conditions Regarding Batch Release Tests for Sterile Drug Products

Conditions	Batch Release Test ○ Test for which FDA generally does **not** intend to take regulatory action under the conditions listed ● Test expected to be performed									
	Identity	**Strength**	**Sterility**	**Endotoxin[c]**	**pH**	**Color**	**Clarity**	**Visible Particulates**	**Subvisible Particulates**	**Other Appropriate Specifications[d]**
Tests are conducted according to these conditions ...										
1. Batch size ≥60 units[a] *or* once 60 units are produced[b]	●	●	●	●	●	●	●	●	●	●
2. Batch size <60 units, if omitted tests are performed once 60 units are produced[b]	○	○	●	●	○	●	●	○	○	○
3. Batch <10 units compounded pursuant to prescription for single patient and label bears BUD per Table D in Appendix B, if omitted tests are performed once 60 units are produced[b]	○	○	○	●	○	●	●	○	○	○
… unless conditions 4, 5, or 6 also apply. If so, choosing the least stringent option for each test among applicable conditions would be consistent with the enforcement policy set forth in this appendix.										
4. Product tested for strength (potency) by method that is highly specific (e.g., HPLC) and uses a reference standard	○	●	●	●	●	●	●	●	●	●
5. For solutions or total parenteral nutrition (TPN) only: - Compounded drug product is single dilution of FDA-approved drug product, or is made from one or more dilutions of FDA-approved drug product performed per labeling dilution instructions and using automated equipment calibrated immediately before and after production - OR - - Bulk solution but not finished drug product is tested for identity and strength immediately before filling into final and prelabeled drug product containers - OR – - Drug product is multicomponent injectable drug product (e.g., TPN product, cardioplegia solution) compounded from APIs produced only by FDA-registered manufacturers, finished product is compounded using automated equipment with validated software, and equipment is calibrated immediately before and after each personnel shift	○	○	●	●	●	●	●	●	●	●
6. Product is terminally sterilized using validated sterilization cycle that uses physical, chemical, or biological indicators	●	●	○	●	●	●	●	●	●	●

[a] Individual tablets or capsules for solid oral dosage forms and suppositories, inserts, or containers (e.g., vial, syringe, IV bag, tube) for other dosage forms.

[b] Omitted tests under this condition need only be performed one time after a single batch of 60 or more units has been produced or once 60 or more units have been produced in more than 1 batch within a year from the time the first batch is produced, and resets once testing has been performed or at 1 year from the time the first batch is produced if a minimum of 60 units was not produced. For example, if the batch size is consistently 35 units (e.g., vials) of a particular volume of drug, testing is conducted on every second batch produced. Or, if the first, second, and third batches in the year include 25, 20, and 30 units respectively, testing is performed on the third batch because the minimum of 60 units has been met.

[c] For finished products compounded from starting materials that are sterile and nonpyrogenic, see section I, Release Testing, for more information on endotoxin testing.

[d] These include generally recognized attributes for each dosage form such as those described in ICH Q6A or USP monographs or general chapters.

APPENDIX B. CONDITIONS UNDER WHICH FDA GENERALLY DOES NOT INTEND TO TAKE REGULATORY ACTION REGARDING STABILITY TESTING AND EXPIRATION DATE REQUIREMENTS

A. Default BUD (No Testing) for Non-Sterile Drug Products: Aggregate Batch Size ≤5,000 Units

FDA generally does not intend to take regulatory action against an outsourcing facility regarding the requirements for stability studies and expiration dates for non-sterile drug products under §§ 211.166 and 211.137 if (1) a BUD has been assigned according to Table C; (2) water activity testing is conducted as described below, if applicable, to determine the type of product for assigning the BUD; (3) literature or other scientific information, including relevant commercially available product labeling for a similar drug (e.g., components, dosage form, route of administration, primary container-closure type), does not indicate that the drug product may not be physicochemically stable over the time period listed; and (4) the BUD is used as the expiration date.[50]

The default BUDs in Table C are based on the likelihood of microbial proliferation as determined by water activity testing. Products with a water activity >0.6 are of greater concern microbiologically because there is potential for proliferation of microorganisms in the product. Use of a validated preservative strategy[51] can greatly reduce the likelihood of microbial proliferation in finished drug products.

Water activity testing is conducted as follows to determine the type of product for assigning the default BUD:

- Solid dosage forms (i.e., tablets and capsules): No water activity testing is necessary.

- Products with water activity >0.6: No water activity testing is necessary if the product is known or assumed to have a high water activity (e.g., liquid oral solution) and the applicable default BUD for products with water activity >0.6 is used.

- Products with suspected low water activity (other than solid dosage forms) (e.g., suppository): Water activity testing is conducted once for each non-sterile drug product formulation according to validated test procedures such as those described in USP General Chapter <1112>. Depending on the results of the water activity test, the BUD should be set according to Table C.

[50] To be eligible for the exemptions provided under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

[51] See USP General Chapter <51>.

Table C: Default BUDs for Non-Sterile Drug Products With Aggregate Batch Size ≤5,000 Units

Type of Product	Storage Conditions	
	Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)
Solid dosage forms	180 days	N/A
Water activity >0.6	Preserved: 30 days Unpreserved: Not applicable	Preserved: 30 days Unpreserved: 14 days
Water activity ≤0.6	90 days	N/A

B. Default BUD (No Testing) for Sterile Drug Products: Aggregate Batch Size ≤1,000 Units

FDA generally does not intend to take regulatory action against an outsourcing facility regarding the requirements for stability studies and expiration dates under §§ 211.166 and 211.137 if (1) a BUD has been assigned according to the criteria based on processing conditions in Table D; (2) literature or other scientific information, including relevant commercially available product labeling for a similar drug (e.g., components, dosage form, route of administration, primary container-closure type), does not indicate that the drug product may not be physicochemically stable over the time period listed; and (3) the BUD is used as the expiration date.[52]

Table D. Default BUDs for Aggregate Batch Size ≤1,000 Units With Given Processing and Storage Conditions

Processing Conditions	Contains a Preservative?	Storage Conditions		
		Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)	Freezer (-25° to -10°C)
• Finished drug product is aseptically processed; and • A sterility test has not been completed before release	No	6 days	9 days	45 days
	Yes	28 days	42 days	45 days
• Finished drug product is terminally sterilized; • A validated sterilization cycle that uses physical,	No	14 days	28 days	45 days

[52] To be eligible for the exemptions provided under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

chemical, or biological indicators is employed; and • A sterility test has not been completed before release	Yes	28 days	42 days	45 days
• Finished drug product is aseptically processed or terminally sterilized and has a completed, passing sterility test before release	No	28 days	42 days	45 days
	Yes	42 days	42 days	45 days

C. Enforcement Policy Regarding the Use of Limited Stability Testing To Assign a BUD

Stability testing is intended to confirm the stability performance of a non-sterile or sterile compounded drug product held under the labeled storage conditions for the duration of the BUD. Procedures established for assessing the stability of drug products compounded by outsourcing facilities must achieve the following (§§ 211.122, 211.160, 211.166):

- Incorporate stability-indicating test methods that are reliable, meaningful, and specific.
- Evaluate samples of the drug product in the same container-closure system and with the same or representative label and adhesive that will be affixed to the container in which the drug product is marketed.
- Evaluate samples for stability that are representative of the batch from which they were obtained and are stored under suitable conditions.
- Incorporate testing to evaluate antimicrobial effectiveness for drug products labeled or intended to be multiple dose. If antimicrobial effectiveness has been previously established for the formulation and container-closure system, a test for preservative content may be used in lieu of a full antimicrobial effectiveness study.

FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing and expiration date requirements if the outsourcing facility uses the approach outlined below describing a number of lots and a set of tests—which should be conducted at lot release as part of normal operations—to be performed at the time of the desired BUD. This section C does not apply to non-sterile unpreserved aqueous drug products because of the higher risk of microbiological proliferation.

The following conditions apply:

- Samples are evaluated following aging under the long-term storage conditions (i.e., temperature and humidity) in ICH Q1A(R2).
- The data from each time point are evaluated against the established specifications for the compounded drug product.

- The BUD is not longer than 12 months.

- If the data for any test fall outside of the established specifications, the BUD is restricted to the last time point at which the data remained within specifications, or the default BUD (described above) is used.

Because of the possibility that a sample may not meet specifications at the final time point, FDA strongly recommends the inclusion of testing at at least one interim time point. If the data at the final time point do not confirm the stability of the product at the desired BUD (e.g., some measurements fall outside of the established specifications), but the data at the interim time point are acceptable (i.e., measurements meet the established specifications), a BUD equal to the interim time point meets the second condition above.

Under this policy, samples from one lot are tested. Each unit subjected to one or more tests that compromise the integrity of the primary container-closure is only tested at a single time point (i.e., not at additional time points). If a single unit is to be used for multiple discrete tests to minimize destructive testing, the unit dosage is subdivided into multiple aliquots that are not held longer than the time to complete the testing (typically not longer than 48-72 hours) and the aliquots are placed into appropriate testing containers (e.g., high performance liquid chromatography vials or sample tubes) that protect the sample from being compromised (e.g., from exposure to air, light, evaporation).

1. Non-sterile

a. Nondestructive tests

The following test is conducted:

- Appearance.

b. Destructive chemical tests

The tests to be conducted include:

- pH, if applicable (e.g., for aqueous formulations).
- Assay.[53]
- Appropriate specifications.

[53] See note 31.

c. Microbiological tests, if water activity >0.6

The tests to be conducted include:

- Antimicrobial effectiveness testing/preservative content testing at expiry.
- Microbial enumeration[54] (USP General Chapter <61>).
- Test for specified organisms[55] (USP General Chapter <62>).

2. Sterile

a. Nondestructive tests

The following tests are conducted:

- Appearance.
- Color and clarity.
- Visible particulates.

b. Destructive chemical tests

The tests to be conducted include:

- pH, if applicable (e.g., for aqueous formulations).
- Assay.[56]
- Subvisible particles (10µm–100µm).[57]

c. Sterility or container-closure integrity tests

To confirm that sterility is maintained over the proposed BUD, container-closure integrity testing (such as described in USP General Chapter <1207>) or a sterility test (see USP General Chapter <71>) is conducted. When performed, container-closure integrity testing is conducted on a number of units that is suitable for the chosen test method.

D. Bracketing

Use of bracketing in stability studies allows for more streamlined evaluation of drug products for which there are multiple strengths or volume presentations produced. Bracketing assumes that the stability of intermediate strengths (or intermediate fill volumes) is adequately represented by

[54] See, for example, USP General Chapter <1111>.

[55] Ibid.

[56] See note 31.

[57] Applicable only to intrathecal, intravenous, intra-arterial, ophthalmic, intramuscular, sterile otic, and subcutaneous preparations.

the extremes tested.[58] For multiple drug products to be eligible for bracketing stability studies, the candidate formulations should vary only in strength (or concentration) or fill volume. Although individual excipient amounts may vary, all excipients (in worst-case amounts) should be in all bracketed formulations. Proportional formulations are not required. The same container-closure system must be used (§ 211.166). If three or more strengths, concentrations, or volume presentations exist, intermediate cases for stability studies as follows may reflect an appropriate use of bracketing:

- If 3 or 4 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes (e.g., if available strengths include 2.0 mg/mL, 3.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL, test 2.0 mg/mL and 10.0 mg/mL).

- If 5-10 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes and 1 intermediate case.

- If more than 10 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes and 2 intermediate cases.

It is critical that determination of the extremes be done with care. For example, with respect to volume fill, the appropriate extremes are not necessarily always the highest and lowest fluid volume fills. Rather, the head space-to-fluid volume ratio may better represent the appropriate extreme depending on the container volume used in the various presentations.

Bracketing as described in this section does not apply to microbial testing of sterility, endotoxins, or bioburden. Bracketing may be appropriate for water activity testing and antimicrobial effectiveness testing when used in conjunction with a preservative content testing strategy.

[58] See ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products* for more information on bracketing and matrixing.