Guidance for Industry

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

DRAFT GUIDANCE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)

July 2014
Current Good Manufacturing Practices (CGMPs)

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This interim guidance describes FDA's expectations 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 final regulations are promulgated, this guidance describes FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 during this interim period. This guidance is only applicable to drugs compounded in accordance with section 503B.

FDA's guidance documents, including this guidance, 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.

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) 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.

II. BACKGROUND

The Drug Quality and Security Act adds a new section 503B to the FD&C Act.[3] Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded in a registered outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act[4] and the requirement to label drug products with adequate directions for use under section 502(f)(1) of the FD&C Act[5] if the requirements in section 503B are met.[6] Outsourcing facilities will be inspected by FDA and must comply with other provisions of the FD&C Act, including CGMP requirements under section 501(a)(2)(B).

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

> the 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 chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess . . . .

Further, section 501 of the FD&C Act, as amended by the Food and Drug Administration Safety and Innovation Act,[7] states

> for the 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.

Generally, CGMP requirements for finished drug products are established in 21 CFR parts 210 and 211.

FDA intends to develop specific CGMP regulations applicable to outsourcing facilities. Until those new regulations are promulgated, this guidance describes FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 during this interim period.

This interim guidance reflects FDA's intent to recognize the differences between compounding outsourcing facilities and conventional drug manufacturers, and to tailor CGMP requirements to the nature of the specific compounding operations conducted by outsourcing facilities while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products.

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

[4] 21 U.S.C. 355.

[5] 21 U.S.C. 352(f)(1).

[6] Drug products produced in accordance with section 503B are also exempt from the track and trace requirements in section 582 of the FD&C Act.

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

FDA intends to focus its inspectional and enforcement efforts on those aspects of outsourcing facility compounding operations that pose the highest risk to patient safety. In particular, the primary focus of this guidance is on those aspects of 21 CFR part 211 that relate to sterility assurance of sterile drug products and the safety of compounded drug products more generally, with respect to strength (e.g., subpotency, superpotency), and labeling or drug product mix-ups.

III. CGMP FOR OUTSOURCING FACILITIES

A. Facility Design

21 CFR part 211, "Current Good Manufacturing Practice for Finished Pharmaceuticals," sets out the requirements applicable to the design of facilities used in the manufacture, processing, packing, or holding of a drug product (§ 211.42).[8] Certain elements of facility design are considered critical to ensuring the quality of compounded sterile drug products. For example, all processing and controlled areas must be clean and free of visible signs of filth, dirt, mold or mildew, insects, and inappropriate items or debris (see also, § 211.56). In addition, the following elements should be met by outsourcing facilities:

- Damaged, dirty, or discolored HEPA filters should not be used.
- Sterile drugs should be produced only in ISO 5 or better air quality (see Table 1).

Table 1 describes cleanroom classification standards as established in ISO 14644-1 Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness.

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

Class Name		Particle Count	
ISO Class	**U.S. FS 209E**	**ISO, m^3**	**FS 209E, ft^3**
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3,520	100
6	Class 1,000	35,200	1,000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

*Limits are in particles of 0.5 µm and larger per cubic meter [current ISO] and cubic feet measured under dynamic conditions. Adapted from former Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 14644-1:1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3,520 particles of 0.5 µm per m^3 or larger (ISO Class 5) is equivalent to 100 particles per ft^3 (Class 100) (1 m^3 = 35.2 ft^3).

- 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[9]). The

[8] In this section, unless otherwise indicated, all references to "§" or "section" refer to Title 21 of the Code of Federal Regulations.

[9] A *critical area* is an area designed to maintain sterility of sterile materials. See FDA guidance for industry, *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

facility layout, room separation, and process flow should be designed in a manner to prevent the influx of contamination from adjacent areas and rooms of lower air quality, and to avoid any disruption of HEPA unidirectional flow.

- The air cleanliness classification of the area surrounding the ISO 5 zone immediately adjacent to the aseptic processing line should meet, at a minimum, ISO 7 (Class 10,000) standards.
- If an isolator is used, the surrounding area should meet at least ISO 8 (Class 100,000) standards.

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

- Airflow studies should be conducted under dynamic conditions (e.g., in-situ smoke study) to initially qualify the HVAC/HEPA unit *and* when any changes are made to the HVAC/HEPA unit or the critical area that might affect airflow. Any indication of poor air control (e.g., non-laminar, turbulent) should be corrected before use.
- HEPA periodic testing/recertification should be performed at least twice a year to ensure that appropriate air flow and quality is maintained. These tests should include integrity testing of the HEPA filters, particle counts, and air velocity checks.
- Velocities of unidirectional air should be measured six 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, re-qualification should be performed before resuming sterile compounding in the unit.

The clean areas in which components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred should be designed to minimize the level of particle contaminants in the final product. The microbiological content (bioburden) of articles and components that are subsequently sterilized should be controlled.

B. Control Systems and Procedures for Maintaining Suitable Facilities

To prevent contamination or mix-ups during the course of sterile and other operations, § 211.42 requires separate or defined areas or other similar control systems for a facility's operations.[10] 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. In addition to the requirements in §§ 211.42 and 211.56, the following control systems and procedures are considered critical to ensuring the quality of compounded sterile drug products and should be implemented at outsourcing facilities:

[10] For example, this would be necessary when using powders because of how the powder particles can drift in the air. However, such separation may not be needed if working with a non-sterile liquid (at that processing step).

- Large equipment present in the cleanroom should not obstruct air vents and/or air flow to compromise aseptic operations.
- Pressure differentials, humidity, and temperatures

Pressure differential limits should be established, and control systems should include built-in alarms to detect excursions. Monitoring for pressure differentials, humidity, and temperatures should occur during production, and prompt action should be taken to correct inappropriate conditions. If a problem cannot be immediately corrected, production should stop until corrected.

Monitoring procedures should require documentation and investigation of any instances in which there is a loss of positive pressure in the clean room during actual production, the lots affected, and the corrective action taken. System alarms may not be necessary if differentials are regularly checked during operations (checks should be scheduled considering the environment, such as use of an isolator versus a less protected process) and the results recorded in logs and evaluated against pre-specified alert and action limits at each check.

- Powder drugs

If powder drugs are handled, procedures should be established and followed to appropriately manage cross-contamination risk, particularly 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/beta-lactam products, a separate facility (or physically separate space) is required (see § 211.42(d)).

- Multiple manipulations, multi-use facilities

Processes and procedures should minimize contamination risks posed by, for example, the number and complexity of manipulations, number of simultaneous operations and workstations, and the staging of materials used in the process.

For multi-use facilities and non-dedicated equipment, changeover and cleaning procedures should be established and followed to prevent cross-contamination between products.

- Cleaning and disinfection of clean areas and equipment sterilization

Procedures for cleanroom cleaning and disinfecting should be established. Procedures for cleaning and disinfecting ISO 5 areas/units should include instructions for consistently and properly cleaning and disinfecting surfaces that are difficult to access. Sterile disinfectants and lint-free sterile wipes should be used for disinfecting all critical areas. Procedures should describe the methods and schedule for cleaning and include the use of sporicidal disinfectants in the ISO 5 area and classified rooms on a regular basis.

The suitability, efficacy, and limitations of the disinfecting agents being used should be monitored. The expiration dates of disinfection solutions should be closely monitored. Published literature and supplier certificates can be relied on when initially determining the

effectiveness of agents used to clean and disinfect the facility and equipment surfaces provided that the supplier's cleaning procedures are followed.

Critical equipment surfaces that come in contact with sterile drug products, containers, and closures should be sterile; disinfection alone is not sufficient (see section D below).

Based on the results of environmental monitoring (see section C below), the sanitation program and other practices should be revised if there are indications that the frequency of disinfectant use or the type of disinfectant being used is inadequate to ensure appropriately clean surfaces.

C. Environmental and Personnel Monitoring

21 CFR 211.42(c)(10)(iv) requires establishing a system for monitoring environmental conditions in aseptic processing areas, while §§ 211.113(b) and 211.28(a) require personnel sanitation practices and gowning to be both acceptable and qualified for the operations they perform. Procedures for monitoring the environment and personnel for the presence of viable particles[11] and non-viable particles should be established and followed as described here.

Environmental monitoring should consist of a well-defined program that evaluates the potential routes of microbial contamination of the human drug that could arise from the air, surfaces, process, operation, and personnel practices. The program should contain an appropriate detection component to verify state of control of the environment. In particular, the program should achieve the following:

- Cover all production shifts and include monitoring during normal production conditions
- Include at least daily monitoring of the ISO 5 zone during operations
- Establish alert and action limits and appropriate responses to each
- Describe use of sampling (e.g., contact plates, swabs, active air samplers), alert and action limits, 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
- Be supported by an evaluation of the choice of the sampling locations and sampling methods

Personnel monitoring should consist of a well-defined program that does the following:

- Includes a routine program for daily/shift monitoring of operators' gloves and an appropriate schedule for monitoring gowns during operations
- Establishes limits that are based on the criticality of the operation relative to the contamination risk to the product

[11] A *viable particle* is a particle that consists of, or supports, one or more live microorganisms (see ISO 14644-6:2007; Cleanrooms and Associated Controlled Environments-Part 6: Vocabulary).

- Calls 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

Procedures should include establishing the validity of the microbiological media, including the preparation, sterilization, and growth potential of the media used in performing tests, including environmental and personnel monitoring.

D. Equipment, Containers, and Closures

Several provisions of part 211 address controls over the equipment used to compound and containers and closures in which the compounded drug product is packaged (§§ 211.65, 211.67, 211.80, 211.82, 211.84, 211.87, 211.94, 211.113). A number of equipment and container/closure controls are considered critical to ensuring the quality of compounded drug products and are expected to be implemented by outsourcing facilities.

Equipment, containers, and closures that come into contact with the drug product must be evaluated to ensure adequacy for intended use, including for holding or storing sterilized equipment, containers, or closures to ensure sterility and cleanliness at time of use (see §§ 211.80, 211.84(d)(6), 211.65, 211.67(a)).

If the outsourcing facility does not use pre-sterilized and depyrogenated single-use equipment (e.g., filters, transfer tubing, temporary storage containers) and containers and closures (e.g., vials, syringes), the equipment, containers, and closures must be sterilized and depyrogenated before first use through sterilization and depyrogenation processes that have been validated, that is, demonstrated and documented to consistently achieve the desired result when performed under defined conditions (see §§ 211.67(a), (b) and 211.94(c)).

Each lot of equipment, containers, and closures must be examined to verify identity and tested to ensure conformity with appropriate specifications before use (see §§ 211.84(d) and 211.67(b)). The Agency does not intend to take action against an outsourcing facility regarding the identification or testing of each lot of single-use equipment, 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, non-pyrogenic; (2) the supplier's packaging integrity is verified upon receipt before use; and (3) the certificate of analysis (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 single-use equipment, container, or closure not meeting acceptance requirements must be rejected or not used until rendered suitable for use (see §§ 211.84(d), (e) and 211.67(a)).

The following additional controls are critical:

- Equipment

Equipment must be qualified as capable of performing its intended functions or operations before first use, and procedures for routine calibration and maintenance 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).

- Containers and closures

Scientifically sound and appropriate criteria 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)). Appropriate procedures must be established for testing the containers and closures at the time they are selected to determine whether they meet the criteria for use; the tests and results must be documented (see §§ 211.84(d)(3), 211.184). As part of the selection process, integrity testing of the drug product container closure system should be performed to verify its ability to maintain the quality of the finished drug product and sterility over the expiry period. Integrity testing should be performed again if the supplier or specifications of the container/closure is changed.

Procedures for storage if appropriate, of sterilized containers or closures must be established in a manner to minimize the risk of contamination and to maintain sterility (see § 211.80(a), (b)). After storage for long periods or after exposure to air, heat, or other conditions that might adversely affect the drug product container, or closure, containers and closures must be re-tested or re-examined for identity, strength, quality, and purity (see § 211.87). However, the Agency does not intend to take action against an outsourcing facility regarding this additional testing if each lot of containers or closures is stored under the supplier's labeled storage conditions and protected from contamination when portions of the lot are removed.

E. Components

Controls over the source and quality of components are required, particularly when using non-sterile materials, or ingredients when producing compounded drug products, especially sterile drug products (§§ 211.82, 211.84, 211.87, 211.113). The following controls are considered critical to ensuring the quality of compounded drug products and are expected to be implemented by outsourcing facilities.

Appropriate specifications must be established for the components used in each drug product (see § 211.160(b)). Specifications should address the attributes necessary to ensure the quality of the finished drug product. Attributes can include: identity, strength, purity, particle size, sterility, bacterial endotoxin level, or other characteristics that could affect the quality of the final drug product.

Each lot of components must be tested to verify identity and evaluated for conformity with appropriate specifications before use (see § 211.84). The Agency does not intend to take action

against an outsourcing facility regarding the identification or testing of each lot if all of the following conditions are met:

- The component is an approved finished human drug product.
- The component was purchased directly from a manufacturer who has registered and listed with FDA under section 510 of the FD&C Act without repacking or other alteration since initial manufacture, or was purchased from a distributor that certifies that the component has not been subject to repacking or other alteration since initial manufacture.
- The label of each lot of the component has been examined to verify that the component meets required specifications before use.
- The shipment's package integrity has been verified upon receipt before use.

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

Components (e.g., bulk active ingredients and excipients, but not an approved finished drug product), must be tested to verify identity and evaluated for conformity with appropriate specifications, and, if necessary, depending on intended use, endotoxin level and sterility before use in compounding (see § 211.84). As described in § 211.84(d)(2), in lieu of testing each shipment of each ingredient, a COA can be accepted from the supplier and evaluated to determine whether the lot can be used, provided that the following conditions are met:

- The reliability of the supplier's analyses has been established at appropriate intervals (i.e., no less frequently than annually for active ingredients and every two years for other components) through appropriate steps to confirm the supplier's test results for those tests relevant to the specifications established for the compounded drug product, and to confirm that the ingredient meets the applicable USP or NF monograph, if one exists.[12]
- At least one identity test has been conducted 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.

Acceptance of incoming lots of nonsterile components (including water) must include microbial and endotoxin testing (see § 211.84(d)(6)). The Agency does not intend to take action against an outsourcing facility regarding this testing if the water is purchased and certified as sterile and non-pyrogenic, and is accompanied by a COA. The quality of water produced on-site and used as

[12] Components (bulk drug substances and other ingredients) used in compounding must comply with the standards of the applicable US Pharmacopeia or National Formulary monograph, if such monograph exists (see sections 503B(a)(2)(B) and (a)(3) of the FD&C Act).

a component or processing aid should be tested regularly at point of use to verify acceptable microbial quality and endotoxin limits.

Components must be re-tested 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 supplier's labeled re-test or expiration date, and protected from contamination when portions of the lot are removed.

Alternative Approach for Comment
Reducing the Need for Laboratory Testing of Incoming Components

FDA is requesting public comment on possible alternative approaches that would enable an outsourcing facility to have confidence in the quality of incoming components without periodic laboratory testing following initial qualification testing to confirm the information in the supplier's certificate of analysis (COA). For example, FDA is considering the following possible alternative approach that could reduce the need for duplicative testing by multiple outsourcing facilities. Comments are requested on this or any other possible alternative approaches.

Under this potential alternative approach, FDA would not intend to take action against an outsourcing facility regarding additional testing to confirm the supplier's COA if (1) the supplier submits to FDA a drug master file (DMF) containing the information outlined below, (2) FDA has reviewed the DMF and issued a letter to the DMF holder stating that FDA has no further comments, (3) the DMF holder has provided a copy of that letter to the outsourcing facility, and (4) the outsourcing facility maintains a copy of the letter that can be produced during an inspection. To avoid devoting resources to reviews of DMFs that would never be relied upon, FDA would only review the DMF upon receipt of a letter from an outsourcing facility indicating its intent to rely on the DMF to fulfill its component testing requirements.

If the supplier is the original manufacturer of the component, the supplier's DMF would need to contain the following current information:

- A description of the testing performed before release and shipment of a component lot to the outsourcing facility and the specific quantitative (or qualitative, if applicable) results of a representative lot
- A description of packaging, labeling, tamper-evident seals, and other features used to ensure package integrity while in distribution
- Examples of testing records, such as chromatographs and spectrographs
- A commitment to update the DMF if any testing performed is significantly modified
- A commitment to notify outsourcing facilities 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

If the supplier is not the original manufacturer of the component (e.g., the supplier is a repackager), the supplier DMF would need to contain the following current information:

- A description of the testing performed before release and shipment of a component lot to the outsourcing facility and the specific quantitative (or qualitative, if applicable) results of a representative lot
- A description of quality assurance activities performed, including:
  - how the supplier ensures that the original manufacturer of the component has not changed
  - how new sources (i.e., other than the original manufacturer) of components are qualified
  - a commitment to convey the identity of the manufacturer of each lot (i.e., within the COA) to the outsourcing facility
  - a commitment to state in each COA that the ingredient was transported through a supply chain fully known to the supplier
  - how often a source is requalified to ensure acceptable quality on an ongoing basis
- A description of packaging, labeling, tamper-evident seals, and other features used to ensure package integrity while in distribution
- Examples of testing records, such as chromatographs and spectrographs
- A commitment to update the DMF if the procedures described above are significantly modified
- A commitment to notify component purchasers 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

F. 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). The following controls are considered critical to ensuring the quality of compounded sterile drug products and are expected to be implemented by outsourcing facilities.

1. General Production and Process Controls

Written procedures for production and process control must be established 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 procedures should ensure documentation that all key process parameters are controlled and that any deviations from the procedures are justified.

Batch records must provide complete documentation of production of each batch of drug product (see § 211.188). The actual batch output (yield) should be compared to the projected (calculated) output for each drug product. If the actual output is different than expected after accounting for sampling and known process loss, this finding should be considered an indicator of a potential problem with production and should be investigated. An acceptance level for actual output

should be established that ensures lot-to-lot consistency. Failure to meet the acceptance criterion must be investigated before approving lot release and may require that the lot be rejected (see § 211.192).

If a drug product intended to be sterile is not terminally sterilized, it is critical that in-process controls include sterile filtration (see § 211.113(b)), preferably just before filling into the final product container.

Storing or holding materials during processing (e.g., prior to sterilization; post-sterilization prior to container fill), also called *hold times*, must be assessed (see §§ 211.110(c), 211.111). Hold time(s) for production phases for a drug product should be limited. Limits should be supported by data and based on an understanding of the associated risk of increased bioburden and increased level of endotoxin. Hold time assessments can be performed as part of the process for validating sterility assurance.

2. Aseptic Drug Processing

Introductory training on 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. An individual would be considered qualified to conduct aseptic operations after having passed at least three successful, successive media fill simulations designed to verify the adequacy of their technique and behavior. Simulations of production should be conducted in the same area where production occurs.

Techniques intended to maintain sterility of sterile 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 during production or, when needed, changed.
- Sterile and non-particle shedding gowning components should be used. Gowning components should be stored such that their sterility is not compromised.
- If an element of a gown is found to be torn or defective, it should be changed immediately.
- Sterile products, containers, closures, or 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 entire body and objects out of the path of unidirectional airflow above 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 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, container-closures, or the surrounding environment.
- In-process material, including intermediates such as stock solutions, should be placed in container-closures that protect the material from the cleanroom environment. Container-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 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 air 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 (e.g., holding vessels, filling equipment, lyophilizer) and periodic verification activities and results must be documented (see § 211.113(b)). Specifically:

- For sterile drug products that are terminally sterilized, validation should demonstrate that the sterilization process achieved at least a 10^{-6} sterility assurance level (SAL) using an appropriate biological indicator.
- For aseptic processing of sterile drug products (i.e., not subjected to terminal sterilization), validation should be demonstrated by conducting media fills simulating the actual production process.
- For aseptic processing (e.g., filling) of sterile powders, validation should be demonstrated by conducting media fills simulating the actual production process.
- For sterile drug products that are filter sterilized, prefiltration bioburden and endotoxin limits should be established and measured prior to sterile filtration. A pharmaceutical sterilizing-grade filter should be used, and filter integrity testing should be conducted after each filtration or production run.
- For sterile drug products that are not subjected to overkill terminal sterilization, pre-filtration bioburden limits should be established and measured prior to filtration.

Media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge 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)
- Lyophilization, when applicable
- Aseptic assembly of equipment (e.g., at start-up, during processing)
- Number of personnel and their activities
- Representative number of aseptic additions (e.g., charging 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., sizes, type, compatibility with equipment)
- Specific provisions in written procedures relating to aseptic processing (e.g., conditions beyond which discarding of exposed materials in the ISO 5 area or line clearance is mandated)

G. 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 (see § 211.160(b)) and should include at a minimum:

- Identity and strength of the active ingredient
- For drug products purporting to be sterile, a limit for visible particles

- For drug products purporting to be sterile and/or non-pyrogenic, sterility and a limit for bacterial endotoxins

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)):

- Except as described below, an appropriate laboratory determination has been conducted to ensure that each batch of a drug product conforms to specifications.
- Associated laboratory data and documentation have been reviewed by the quality control unit and demonstrate that the drug product meets specifications.
- A designated qualified individual from the quality control unit has authorized final release.

The Agency does not intend to take action against an outsourcing facility regarding the release testing requirements described above, under the following conditions:

- For testing to confirm identity, if specifications have been established and met for strength (potency).
- For sterility testing, if the drug product is terminally sterilized and a validated sterilization cycle that uses bioindicators is employed.
- For sterility testing, if it is *initiated before* batch release (see also Subsection I "Stability/Expiration Dating," below, for information on how to label products released without a completed sterility test) and
    - procedures have been established that specify that if the drug product fails to meet a criterion for sterility, all facilities that received the drug product will be immediately notified of the test results and provided with any appropriate information and recommendations to aid in the treatment of patients;
    - the notification will be documented; and
    - FDA will be notified in writing.[13]
- For sterility testing, if the batch consists of fewer than 10 dosage units[14] compounded pursuant to a prescription for a single patient, and the unit(s) is labeled with a beyond use date (BUD), where the BUD provides reasonable assurance of chemical and physical stability based on literature or other scientific information, and is established according to the following:
    - not to exceed 24 hours at USP controlled room temperature;
    - not more than 3 days refrigerated;
    - not more than 45 days in a solid frozen state between -25° and -10°.

[13] Reports should be submitted to FDA electronically to OFAlertReport@fda.hhs.gov.
[14] One dosage unit is the amount of drug in a labeled dose, e.g., one tablet or one syringe.

If the batch size is very small and does not meet the criteria above for eliminating the sterility test when compounding pursuant to a prescription for a single patient, standard sterility tests may require that additional units be produced to be able to conduct the sterility test. For example, USP <71> "Sterility Tests" is the principal source used for sterility testing methods, and requires that the number of samples for batches of parenteral drug products containing less than 100 containers be 10% or 4 containers, whichever is greater. However, the Agency does not intend to take action against an outsourcing facility regarding the number of units tested if 10% of the containers in the batch is less than 4, and the sterility test is conducted using a number of containers that equals 10% rounded up to the next whole number.

With regard to testing other than sterility testing, for batches of less than 10 units, since complete release testing would require use of a significant proportion of the batch, the Agency does not intend to take action against an outsourcing facility regarding testing on every batch to demonstrate conformity with other specifications such as identity, strength, and particulate, if such testing is performed on samples from every other batch, or once at least 10 units of that drug product have been produced. For example, if the batch size is consistently 5 units, testing should be conducted on every second batch. As another example, if the first batch is 5 units, the second batch is 3 units, and the third batch is 3 units, testing should be performed on the third batch because the minimum of 10 units has been met.

For aqueous solutions, testing for identity and strength can be performed on the bulk solution just before filling the finished drug product containers.

H. Laboratory Controls

When testing components, in-process materials, and finished drug products, laboratory controls must be used to ensure the reliability of the tests (§ 211.160). Each laboratory, whether in-house or external[15] to the outsourcing facility, used to conduct testing of components, in-process materials, or finished drug products must employ the following critical aspects of laboratory controls to ensure the quality of 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
- Have sampling and testing procedures designed 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

[15]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 21 CFR 200.10(b); 21 CFR 211.22(a); and FDA draft guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM353925.pdf.

- Keep complete records of all tests performed to ensure compliance with established specifications and standards, including examinations and assays

Alternative Approach for Comment
Minimize Need for Facilities to Have an In-House Laboratory

FDA is requesting public comment on a possible alternative approach that would minimize the need for outsourcing facilities to establish an in-house laboratory to perform final release testing, while providing confidence about the accuracy of testing performed by a third-party. For example, FDA is considering the following possible alternative approach. Please comment on this or any other alternatives.

A laboratory interested in performing testing for outsourcing facilities could submit a drug master file (DMF) containing the information outlined below. Upon receipt of a letter from an outsourcing facility stating its intention to use the laboratory, FDA would review the DMF. If the review did not identify any questions regarding the content of the DMF, FDA would issue a letter to the DMF holder stating that FDA has no further comments. A copy of that letter would need to be provided to and be maintained by the outsourcing facility and produced during an inspection. Laboratory DMFs would need to contain the following:

- A description of the procedures for the conduct and documentation of each test to be conducted
- A description of how the methods and equipment for each test were found to be suitable for their intended use and capable of producing valid results
- A description of records to be maintained at the laboratory and/or provided to the outsourcing facility (e.g., out-of-specification (OOS) investigation)
- A description of the quality assurance activities performed, including:
  - qualification of lab analysts and their supervision
  - verification that analytical results reported to customers are accurate and complete
  - procedures for handling unexpected and out of specification results
  - maintenance of equipment used in testing, data analysis, and data storage
  - controls to ensure data integrity
- A commitment to update the DMF if the procedures described above are significantly modified
- A commitment to notify outsourcing facilities of specified changes or problems, such as investigations of its operations resulting from an OOS finding, a change in test method, or identification of an error in test results provided to the outsourcing facility

I. Stability/Expiration 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 (21 CFR 211.166). Stability testing is used to ensure that a drug product will retain its quality (for example, strength[16]) and remain sterile through the labeled expiration date. Procedures established for assessing the stability of drug products compounded by outsourcing facilities should achieve the following:

- Incorporate stability-indicating test methods that are reliable, meaningful and specific
- Evaluate samples of the drug product in the same immediate container closure system and with the same label that will be affixed to the container when the drug product is marketed
- Evaluate samples for stability that are representative of the lot or batch from which they were obtained and are stored under suitable conditions
- Incorporate testing to evaluate antimicrobial effectiveness (resistance to antimicrobial contamination) for drug products labeled or intended to be multiple dose
- Evaluate three (3) batches of each drug product to determine the expiration date

The Agency does not intend to take action against an outsourcing facility regarding stability studies if (1) a beyond-use date (BUD) has been established according to the bulleted criteria below, (2) the BUD provides reasonable assurance of chemical and physical stability based on literature or other scientific information, and (3) the BUD is used as the expiration date.[17]

- If the finished drug product is terminally sterilized and a sterility test has not been completed before release, the drug product is labeled with a BUD of not more than 14 days.

- If the finished drug product is aseptically processed and a sterility test has not been completed before release, the finished drug product is labeled with a BUD
  - not to exceed 24 hours at USP controlled room temperature;
  - not more than 3 days refrigerated;
  - not more than 45 days in a solid frozen state between -25° and -10°.

- If each batch of the finished drug product has a completed sterility test before release, the finished drug product is labeled with a BUD of not more than 14 days (at USP controlled room temperature or refrigerated) or not more than 45 days (in a solid frozen state between -25° and -10°) beyond completion of the sterility test (e.g., for a sterility test that takes 14 days to complete, the BUD would not exceed 28 days at USP controlled room temperature).

[16] For more information on strength and stability testing, see Allen Jr. L, Bassani G, Elder Jr. E, Parr A, for the USP Compounding Expert Committee. Strength and Stability Testing for Compounded Preparations.

[17] Under section 503B(a)(10)(A)(iii)(VI) of the FD&C Act, the compounded drug product must be labeled with an expiration date.

- Notwithstanding the conditions outlined above, for sterile preserved drugs, the finished drug product is labeled with a BUD of not more than 30 days beyond completion of the sterility test.

In addition, the Agency does not intend to take action against an outsourcing facility regarding stability testing if the drug product is composed solely of one or more drug products approved under section 505 of the FD&C Act, the approved drug product labeling specifies how to assign an *in-use time,* the compounded drug product has been compounded and labeled with an *in-use time* in accordance with the approved product labeling, and the in-use time is used as the expiration date. If two or more approved drug products are used in the compounded drug product, the in-use time for the compounded drug product should be the shortest of the in-use times specified by the drug product labeling.

If the drug product requires additional manipulation before administration or the labeling permits multiple entries of the container/closure system, appropriate studies should be conducted to support the labeled in-use time.

J. Packaging and Labels

Packaging of sterile drugs must be appropriate to the product and capable of ensuring the sterility 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 sterile drug products and are expected to 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 or any intermediate such as a stock solution (e.g., cracked vials, pinhole leaks in bags, frozen drug products).
- Adequate controls have been established for issuing labels, examining issued labels, and reconciliation of used labels to prevent mix-ups.
- There is physical/spatial separation between different labeling and packaging operations to prevent mix-ups.
- Adequate controls have been established to ensure proper identification of any filled containers of sterile drug products that will be stored unlabeled for any period of time.
- Packaging records include specimens of all labels used.
- The labeled finished drug product has been examined for accuracy and thoroughness before release.

K. Quality Assurance Activities/Complaint Handling

Quality assurance activities are needed to ensure that procedures are followed and a quality drug product is produced (§§ 211.22, 180, 192, 198). Part 211 requires that drug producers establish a quality control unit to oversee various aspects of sterile production.

It is expected that the quality control unit 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 the responsibilities handled by production personnel. In very limited circumstances, a single individual can perform both production and quality functions. That person is still accountable for implementing all the controls and reviewing the results of compounding operations to ensure that product quality standards have been met. Under such circumstances, it is recommended that another qualified individual, not involved in the production operation, conduct an additional, periodic review of quality control unit activities.

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 drug products and are expected to be implemented by outsourcing facilities.

The quality control unit is responsible for discrepancy and failure investigations and the development and oversight of appropriate corrective actions and preventive actions regarding the following:

- Rejected lots of finished drug product, including initial positive sterility tests or out-of-specification results for attributes such as endotoxin level, assay, impurities, particulate matter, or reconstitution time, if applicable and regardless of batch disposition
- Unexpected results or trends
- Failures that occurred during validation or revalidation of sterilization or depyrogenation processes, including media fill/process simulation failures
- Stability failures, including failures of quality that are determined to have other causes 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 and lyophilizers
- Returned goods that indicate possible drug product contamination or other risks to patients (e.g., hazy or cloudy drug product, foreign matter/particulates in injectable drug products, cracked or leaky containers)

The quality control unit has the responsibility to ensure 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)).

The quality control unit must periodically 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:

- For aseptic processing, all media fills/process simulations performed since the last review
- Results of environmental monitoring
- Results of personnel monitoring
- Results of water system testing, where water is used as a component in the drug product and is purified/processed on-site
- Results of finished drug product testing
- Periodic scrutiny of operations to ensure adherence to procedures and proper aseptic technique

The quality control unit is also responsible for evaluating written and oral complaints concerning the quality or purity of, or possible adverse reactions to, a drug product. Complaint handling procedures must include a determination as to the need for a full investigation and provisions for review to determine whether the complaint represents an adverse event that must be submitted to FDA (see §§ 211.198 and 310.305, and section 503B(b)(5) of the FD&C Act).

REFERENCES

The following references provide additional information regarding the recommendations outlined above.

ISO 14644-1 "Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness."

ISO 14644-6:2007 "Cleanrooms and Associated Controlled Environments – Part 6: Vocabulary."

FDA guidance for industry, *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*.[18]

FDA guidance for industry, *Contract Manufacturing Arrangements for Drugs: Quality Agreements.*

FDA guidance for industry, *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production.*

Allen Jr. L, Bassani G, Elder Jr. E, Parr A, for the USP Compounding Expert Committee. Strength and Stability Testing for Compounded Preparations. Available at http://www.usp.org/sites/default/files/usp_pdf/EN/2014-01-13__strength_versus_stability_testing_for_compounded_preparations_3.pdf.

[18] FDA guidance documents are available on the FDA webpage at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

GLOSSARY

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

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

Alert Limit – An established microbial or airborne particle limit 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 Process– the process by which a sterile product is packaged in a sterile container in a manner that maintains sterility.

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

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 is intended to notify 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 prior to 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 upon its resistance to the given process. Incoming lot D-value and microbiological count define the quality of the BI.

Cleanroom – A room designed, maintained, and controlled to prevent particle and microbiological contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.

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.

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

Depyrogenation – A process used to destroy or remove pyrogens (e.g., endotoxin).

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

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 upon product-specific studies evaluating the specific formulation of a drug product, the specific container in which it is to be stored, and 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.

HVAC – Heating, ventilation, and air conditioning.

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

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.

Isolator – A decontaminated unit, supplied with Class 100 (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).

Laminar Flow – An airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight line vector.

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.

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.

Terminal Sterilization – The application of a lethal agent 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 nonsterile unit of greater than one in a million).

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