

CHAPTER 56 – DRUG QUALITY ASSURANCE

SUBJECT:  STERILE DRUG PROCESS INSPECTIONS		IMPLEMENTATION DATE November 5, 2012
		COMPLETION DATE November 5, 2015
DATA REPORTING		
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
Industry codes 54, 56 and 60-66 inclusive	Domestic / Foreign Inspections: 56002A (Full Inspection) 56002I (Abbreviated Inspection)  Related PACs  56002 56002C 56002M	

**FIELD REPORTING REQUIREMENTS:**

As soon as the District becomes aware of any significant inspectional, analytical, or other information developed under this program that may affect the agency’s new drug and abbreviated new drug approval decisions with respect to a firm, the District should report the information immediately according to current FACTS and EES procedures. This includes promptly filing and changing OAI notifications.

Forward a copy of each Establishment Inspection Report (EIR) for inspections classified as Official Action Indicated (OAI) due to current good manufacturing practice (CGMP) deficiencies as part of any regulatory action recommendation submitted to CDER Office of Compliance. For all domestic inspections that result in a recommendation to CDER for regulatory action based on current good manufacturing practice deficiencies, forward the recommendation and any associated documentation to CDER and other offices as specified in the Regulatory Procedures Manual. Warning Letter recommendations, with a copy of the proposed Warning Letter and supporting documents, should be sent to CDER Office of Manufacturing and Product Quality (OMPQ), Division of Domestic Drug Quality (DDDQ) via CMS. All other regulatory action (e.g., seizure, injunction) recommendations and associated documentation based on domestic inspection should also be sent to DDDQ.

For all foreign inspections, regardless of inspection outcome, forward the complete and original EIR, including exhibits, to CDER OMPQ, Division of International Drug Quality (DIDQ) in CMS, or send to the following address:

U.S. Food and Drug Administration  
CDER / OMPQ / DIDQ  
10903 New Hampshire Avenue  
Bldg. 51, Room 4218  
Silver Spring, Maryland 20993  
FAX: (301) 847-8738

**NOTE:** Districts should assure that each operation performed by direction of this program circular is entered against the correct Product Code and Program/Assignment Code (P/AC).

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## PART I - BACKGROUND

This program covers the manufacture and testing of all sterile drug products, including drugs that are sterilized by filtration or other means and aseptically processed, and drug products that are terminally sterilized. The type of products covered by this program include sterile bulk drugs, ophthalmic drugs, otic dosage forms, small volume parenteral (SVS) products for small molecule and licensed biological therapeutic drug products, large volume parenteral (LVP) products, and any other drug products required to be sterile or labeled as sterile. Center for Biologics Evaluation and Research (CBER) regulated products and veterinary drug products are excluded from coverage under this program.

The guidance information in this program is tailored to sterile manufacturing operations and should be used in conjunction with the Compliance Program for Drug Manufacturing Inspections (CP 7356.002).

In 2004, Food and Drug Administration (FDA) published the *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing-- Current Good Manufacturing Practice*, which is referred to throughout this Compliance Program as FDA's "2004 Aseptic Processing Guidance." The document represents FDA's current thinking on Current Good Manufacturing Practices (CGMPs) for aseptically processed drugs.

The Guidance for Industry does not establish mandatory requirements and should not be referred to as the justification for an inspectional observation. Justification for inspectional observations originates from the CGMP regulations, 21 CFR Parts 210 and 211.

Manufacturers who follow the 2004 Aseptic Processing Guidance are generally considered compliant with CGMP regulations. However, alternate approaches may be used if such approaches satisfy the requirements of 21 CFR Parts 210 and 211.

For technical questions and unusual circumstances encountered during an inspection, investigators are encouraged to contact their District, ORA Office of Medical Products and Tobacco Operations/Division of Medical Products and Tobacco Program Operations and/or CDER for consultation. For questions concerning microbiological analysis, sterility and related sampling concerns, contact ORA Office of Regulatory Science/Medical Products and Tobacco Scientific Staff.

[end Part I]

## PART II - IMPLEMENTATION

### 2.1 OBJECTIVES

The primary objective of this program is to provide guidance for conducting inspections of manufacturers of sterile bulk<sup>1</sup> and sterile finished dosage drug products to determine compliance with the Food, Drug, and Cosmetic Act and the Current Good Manufacturing Practice Regulations (CGMPs), Title 21, CFR Parts 210 and 211.

Other objectives include:

- Obtain information on operations impacting on sterility, to identify areas for improvement and correction.
- Evaluate current good manufacturing practices in the sterile drug industry.
- Initiate appropriate action against manufacturers observed to be out of compliance.

### 2.2 PROGRAM MANAGEMENT INSTRUCTIONS

#### A. STRATEGY

##### (1) Inspection of Systems

Inspections of drug manufacturers should be made and reported using the system definitions and organization in this compliance program. Focusing on systems will increase inspection efficiency because the systems are often applicable to multiple profile classes. The selection of the system(s) for coverage will be made by the District Office based on the firm's specific operation, previous coverage, compliance history, or other priorities determined by the District Office.

The inspection should normally result in a determination of acceptability or non-acceptability for all profile classes. Coverage of a system should be sufficiently detailed, i.e., select an example of each profile class, so that the conclusion about the system's state-of-control applies to all the profiles classes. However, the determination that a system is adequately controlled for one profile class can be extended to another profile class(es) even if that other profile class(es) was not specifically reviewed. The lead Investigator must consider the uniqueness of the various manufacturing situations at the plant and use their best judgment when selecting profile classes to review.

Selecting specific areas unique functions within a system will be at the discretion of the lead Investigator.

The options for system coverage are described in CPGM 56002. Any given inspection need not cover every system. See [Part III - Inspectional](#).

Complete inspection of one system may necessitate further follow up of some items within the activities of another system(s) to fully document the findings. Such follow up does not constitute full coverage of the other system (and cannot be reported as such in FACTS); nor does that follow up obligate the investigator to perform full coverage of the other system.

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<sup>1</sup> "Sterile bulk" refers to sterile active pharmaceutical ingredients (APIs).

## (2) Inspectional Scope

Inspections of sterile product drug manufacturers are performed as either Full Inspections or Abbreviated Inspections using the systems strategy outlined in Part II –Implementation, of Compliance Program 7356.002, Drug Manufacturing Inspections.

See [Part III – Inspectional](#), of this program for a complete discussion of the coverage requested under these inspection options.

## B. INSPECTION PLANNING

Implement this program when sterile drug manufacturers are inspected as part of a regular statutory inspection. CDER will identify firms for inspection based on the risk-based prioritization model on annual performance goals, as part of the initiative to ensure risk-based prioritization of inspection coverage.

Consider using a team approach for conducting inspections when appropriate. Utilize investigators familiar with sterile drug manufacturing and aseptic processing and consider the participation of a microbiologist with expertise in microbial controls. Specifically,

- All team members should be very familiar with FDA’s Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (September 2004).
- Investigators or team members should be well qualified in sterile product manufacturing, and have completed formal training courses in parenteral drug manufacture, aseptic technique, sterilization methods, and related procedures and equipment. Microbiologists involved should have experience in sterility, endotoxin testing, and evaluation of microbial controls in manufacturing.

## C. PROFILE REPORTING

Update all applicable profile classes in the profile screen of the FACTS coversheet based on inspection findings. The following is a list of sterile product profile classes effective at the time this program was implemented. Use the codes corresponding to the product and process type covered.

PROFILE CLASS	FULL DESCRIPTION
LVP	Large Volume Parenterals are sterile injectable drugs packaged in containers labeled as containing more than 100 mL. Most are terminally sterilized, but some can be sterilized by filtration and aseptically processed.
SVT	Small Volume Parenterals are sterile injectable drugs packaged in containers labeled as containing less than 100 mL that are terminally sterilized.
SVS	Small Volume Parenterals are sterilized by filtration and aseptically processed.
SVL	Small Volume Parenteral are sterilized by filtration, aseptically filled and lyophilized.
SLQ	Sterile liquid (other than suspensions and emulsions)
SON	Sterile ointment
SPW	Sterile powder
CSS	Sterile bulk drugs that are made by chemical synthesis.
CFS	Sterile crude drugs made by fermentation.
CRX	API sterile or API intermediate/NEC inorganic/mineral

[end Part II]

## PART III - INSPECTIONAL

### 3.1 TYPES OF STERILIZATION

There are two broad methods to produce a sterile drug product:

- Terminal Sterilization
- Aseptic Processing of sterilized unit components

There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization. Terminal sterilization should be utilized when the product and container/closure system are able to withstand the terminal sterilization process.

**A. TERMINAL STERILIZATION** - The terminal sterilization process usually involves filling and sealing product containers under high quality environmental conditions designed to minimize microbial and particulate contamination of the product. This minimization of upstream bioburden reduces the challenge to the subsequent sterilization process. In most cases, the product, container, and closure have low bioburden, but are not sterile at the time of filling. The product is then subjected to a sterilization process in its final container.

There are various methods of terminal sterilization including:

- Moist Heat Sterilization
- Irradiation
- Ethylene Oxide (typically for assembled components/kits)

Types of sterilization cycles include:

1. Overkill method:

- Generally used for heat stable materials.
- Designed to provide a significant level of sterility assurance regardless of the number and resistance of the actual bioburden organisms in the load.
- Results in greater heat/exposure input to the product or items being sterilized.

2. Bioburden Based cycle:

- Requires studies to determine the number and resistance of the microorganisms found in the product and the bioburden load of the incoming components and containers/closures.
- Cycle development to destroy the microbial load, but not degrade the product.
- Routine bioburden monitoring of batches and ongoing knowledge of the heat/exposure resistance of organisms found in product bioburden, container/closure bioburden and environmental monitoring samples.

Reference to terminal sterilization: PDA Technical Report No. 1 (Revised 2007) *Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control*.

**B. ASEPTIC PROCESSING** - Aseptic processing presents a higher risk of microbial contamination of the product than terminal sterilization. In an aseptic filling process, the drug product, containers and

closures are sterilized separately and then brought together under an extremely high quality environmental condition designed to reduce the possibility of a non-sterile unit. Aseptic processing involves more variables than terminal sterilization. Any manual or mechanical manipulation of the sterilized drug, containers, or closures prior to or during aseptic filling and assembly poses the risk of microbial contamination.

Some types of aseptic processing involve manual manipulations of sterile components, containers, and closures in addition to routine operator interventions in the critical area. Humans are a significant source of contamination in traditional aseptic processing, especially in production lines that require operators to routinely enter critical areas (Class 100, ISO 5, or Grade A) of the filling line. Aseptic processing systems based on more advanced control-based technologies, such as Restricted Access Barrier Systems (RABS) and Blow-Fill-Seal systems, are designed to reduce human interventions in the critical areas of the fill line while an isolator system completely separates the aseptic filling line from the external environment and minimizes employee interaction with the critical area.

**Note:** More information about Isolator Technology and Blow-Fill-Seal systems is found in FDA's 2004 Aseptic Processing Guidance.

When conducting inspections of sterile drug manufacturers, it is important to cover systems and areas within systems that present the greatest risk of product contamination and/or require strict control of processing parameters. For example, if a firm has several aseptic processing lines, cover the line(s) that require the most manual manipulations in the Class 100 (ISO 5) areas. If the firm terminally sterilizes a number of products, review one that is sensitive to heat and requires a product specific (bioburden based) sterilization cycle.

**Note:** For terminal sterilized products that are aseptically filled prior to terminal sterilization, less rigorous aseptic controls can be considered.

Because of the time limitations often associated with foreign inspections, careful inspection planning is particularly important. Prioritize areas for coverage based upon their potential impact on product quality.

### 3.2 REPORTING

Follow instructions in the current editions of the IOM (*Investigations Operations Manual*) and *Guide to International Inspection and Travel* in preparing the inspection report.

Use Turbo EIR for all reports, both domestic and international, even if a FDA-483 was not issued or was issued outside of Turbo EIR. The "Manufacturing / Design Operations" section of the report should be organized by the systems described in this program that were covered during the inspection. Briefly summarize your review of each covered system in accordance with the key elements outlined in this Compliance Program. Add more details and supporting evidence for the systems found to be deficient.



### 3.3 INSPECTION APPROACHES

If the sterile drug products to be inspected are radioactive drugs, then Compliance Program 7356.002C, *Radioactive Drugs*, should be followed as supplementary guidance. This program should not be used for the inspection of Positron Emission Tomography (PET) Drug. Compliance Program 7356.002P is specific for PET drugs.

This program (CP 7356.002A) should also be used in conjunction with Compliance Program 7356.002M, *Inspection of Licensed Biological Therapeutic Drug Products* for the inspection of sterile licensed biological products.

The CGMP Compliance Program 7356.002 provides general information on the system based approach to conducting inspections of drug manufacturers. It describes the six systems (Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling, and Laboratory) and the two inspection options (Full Inspection and Abbreviated Inspection). It also provides guidance on when each option should be selected and discusses what “state of control” means in relation to the systems inspected.

Inspections of sterile drug manufacturers are performed as either Full or Abbreviated inspections using the systems strategy outlined below.

Full Inspections include surveillance or compliance inspections and provide a comprehensive evaluation of the firm’s compliance with CGMP. A Full Inspection will normally include an inspection of at least four systems, one of which must be the Quality System. Under this program, a Full Inspection should include the Facilities & Equipment, and Production Systems due to the critical role these systems play in the sterility assurance of finished product.

Full Inspections (PAC 56002A) are conducted

- when initial inspection of the drug firm is to be conducted;
- when it is the first inspection conducted as a follow-up to a Warning Letter, regulatory action, or significant FDA 483 findings;
- when information obtained during the Abbreviated Inspection reveals significant deficiencies with the firm’s practices and procedures in one or more system areas;
- when there have been significant changes in the firm’s operations since the last inspection; or
- for surveillance purposes at the District’s discretion because the firm has a history of recurring violations, fluctuating in and out of compliance, or when other information (samples, complaints, Field Alerts, recalls, etc.) calls into question the firm’s ability to produce quality products.

Abbreviated Inspections (PAC 56002I) may be appropriate if the following two conditions are satisfied:

1. the firm has implemented a formal risk management program that assures effective design and control (including maintenance). This includes a risk mitigating design of their processing lines that incorporates a *modern* separation and automation approach (e.g., isolators, closed RABS), and upstream bioburden controls. The responsiveness of the firm’s quality system to potential hazards is also part of the evaluation, including whether the firm’s program provides robust

- daily assurance and effective consumer protection through a formal lifecycle quality risk management program that proactively uncovers and corrects issues in accord with ICH Q9.
2. the firm has a record of sustained acceptable compliance history and a strong risk management program.
    - the firm produces finished drug products that are terminally sterilized using robust sterilization methods. (Note: Terminal sterilization provides a much more robust process to ensure sterility); or,
    - the firm has implemented robust risk management that provides daily assurance through their overall design and control program;
    - at the start of the inspection, conduct an extensive review of sterility assurance data since the last Full Inspection. The review of media fills, sterility testing data, recalls, defect/adverse event complaints, and reports reveals no findings of sterility failure of a distributed batch, and
    - the firm has a record of satisfactory CGMP compliance (e.g., two consecutive NAI or no more than one VAI inspection), with no Class 1 recalls.

Microbial controls and sterility assurance should be the main focus of an abbreviated sterile drug inspection. The following critical elements of each system (other than the Quality System) should be covered in an Abbreviated Inspection under this program:

- Facilities and Equipment:
  - cleaning and disinfection
  - facility/equipment layout and air handling system for preventing viable and non-viable contamination
  - material flow
  - quality control of classified areas, including air pressure balance and HEPA filtration
  - trending data supporting the adequacy of clean room quality
  - documented investigation into discrepancy
- Materials:
  - microbial and bacterial endotoxin control of incoming materials and components
  - quality of water supply, maintenance, qualification
  - operation of the systems that provide the requisite water and process gases
  - documented investigations into OOS, deviations, and discrepancies
- Production:
  - observation of adequacy of operator behavior and aseptic techniques during manufacturing
  - production line operations and interventions
  - personnel training in aseptic techniques
  - major production line repair or maintenance issues
  - risk assessment on microbial and bacterial endotoxin controls, including hold times of critical steps

- validation of sterilization of equipment, container-closures and supplies
- media fills design and results
- documented investigations into, deviations, discrepancies, and OOS results
- Laboratory:
  - investigations into OOS, deviations, and discrepancies
  - test methods and controls, including adherence to validated methods
  - training and qualifications of laboratory personnel
  - trending of water system test results
  - systems used for recovery, identification and trending of environmental monitoring isolates

### 3.4 SYSTEM INSPECTION COVERAGE

Compliance Program 7356.002, *Drug Manufacturing Inspections*, lists the areas that should be covered when inspecting each of the six systems. This program provides additional guidance, by system, for areas of specific concern for sterile drug products.

[Attachment A](#) is a list of questions intended to be an aid in conducting inspections and obtaining information needed to assess a firm's operations. The answers do not have to be reported in the EIR unless they are relevant. The list of questions covers: moist heat sterilization; dry heat sterilization/depyrogenation; aseptic filling; lyophilization; isolators; environmental monitoring; and biological indicators.

### 3.5 QUALITY SYSTEM

As noted in Compliance Program 7356.002, the inspection of the quality system is two-phased. The first phase is to evaluate whether the Quality Unit has fulfilled their responsibility regarding the review and approval of procedures and assured their suitability for use. The second phase is to assess the data collected by the firm to identify potential quality problems. For sterile manufacturing operations, this latter objective involves large amounts of data that link to the other inspectional systems. The comprehensive review of such data by the firm is an essential element in assuring that products are produced with a high degree of sterility assurance. It is therefore important to review the firm's system for using the data to assess the state of control of their manufacturing operations and facility. The data summaries and trend reports maintained by the Quality Unit should be reviewed during every inspection. During a routine CGMP inspection, this review can help determine which option (Full or Abbreviated) to select.

The inspection of the Quality System should include the areas listed in CP7356.002. For this program, the inspection should include a review of all data and reports that may indicate product contamination and sterility assurance issues.

Records pertaining to quality consist of the following:

1. Periodic product evaluations, complaints, adverse events, investigations, Field Alert Reports, product retain evaluations, complaints, rejected lots, stability, and returned goods that indicate

possible product contamination or risks to patients (for example, hazy or cloudy product, foreign matter/particulates in injectable products, cracked, and leaky containers).

2. Discrepancy and failure investigations, such as:

- All initial positive sterility tests and endotoxin and media fill failures regardless of final disposition.
- Unexpected results or trends.
- All failures that occurred during validation or revalidation of sterilization / depyrogenation processes.
- All investigations involving media fills / process simulations.
- Environmental (microbial/viable and particle/non-viable counts) and personnel monitoring results that exceed alert or action levels.
- Process deviations or equipment malfunctions that involve critical equipment, such as sterilizers and lyophilizers.
- Out of Specification (OOS) results for assay, impurities, particulate matter, or reconstitution time, if applicable.
- Product rejects (rejects determined during manufacturing and Quality Control test)

3. Trends reports/ summaries of quality indicators:

- For aseptic processing, summary of all media fills performed since last inspection.
- Environmental monitoring trend data (microbial and particle counts).
- Personnel monitoring trend data.
- Summary of water system test results.

4. Summary of change controls for critical utilities and equipment implemented since the last inspection, for example:

- Sterilizers, lyophilizers, depyrogenation equipment
- Aseptic processing line
- Clean steam generator, process gas system
- WFI and / or Purified Water system
- Air handling systems
- Automated building management system

Every inspection of a sterile drug manufacturer should include a review of the type of information listed above and observation of the manufacturing operations occurring in the critical areas. The information can be used to select other system(s) to be covered during the inspection.

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

### 3.6 FACILITIES AND EQUIPMENT SYSTEM

Compliance Program 7356.002 lists the general areas to cover when inspecting the Facilities and Equipment System. The areas are applicable to sterile drug products and should be covered if this system is selected. The principle objective of an effective sterile drug manufacturing operation from a facility and equipment standpoint is to provide suitable protection of product. The inspectional evaluation of this objective is again two-part:

- Review and evaluate the firm's rationale for, and adequacy of, the facility and equipment design (Reference: Section IV of FDA's 2004 Aseptic Processing Guidance).
- Evaluate the data that provide information relevant to the state of control of the facility and equipment.

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

#### A. FACILITIES

Evaluate the design and layout of the facility (e.g., personnel/material flow, cleanroom design).

Specifications for clean room areas (layout, air filtration, appropriate air classification, pressure differentials between rooms and areas, temperature, and humidity) should be appropriate, and based on the risk of product contamination with particulate matter and microorganisms. Review the certification and qualification of the clean room areas to verify the areas meet design criteria and specifications. Certification and qualification typically includes data in support of the following: air flow pattern studies, HEPA (High Efficiency Particulate Air) filter integrity testing, air velocity measurement, non-viable particle, and verification of appropriate pressure differentials, temperature and humidity setpoints. Evaluate the airflow pattern (smoke studies) conducted under dynamic conditions to verify the unidirectional airflow and air turbulence within the critical area where sterilized drug product, containers, and closures are exposed to environmental conditions.

- Reference: Section IV of FDA's 2004 Aseptic Processing Guidance.
- Routine monitoring and maintenance to assure air handling systems continue to operate within established parameters (microbiological monitoring is discussed under the Laboratory Control System).
  - Afford special attention to facilities that are performing construction in the clean areas, or at the vicinity of cleanroom. Because microbes (e.g., fungal spores) can be liberated from the movement of walls and other construction activities, determine if the facility is returned to acceptable environmental control through proper measures (environmental monitoring, media fills) before production can resume.
  - Verify that environmental monitoring of non-viable particle is occurring during operations including sites where there is the most risk to exposed product, container and closures.

- Check if pressure differentials, temperature, and humidity are continuously monitored during routine production.
  - Determine if continuous monitoring systems are alarmed to alert operators of excursions.
  - Check if excursions from acceptable ranges are investigated to determine impact on product and that needed corrective actions are taken.
  - Evaluate the program for periodic testing / recertification of the HEPA filters in critical areas to maintain appropriate air flow. The tests typically include integrity testing of the HEPA filters and air velocity checks.
- Sanitization / disinfection of clean room areas, processing lines, and non autoclavable equipment, materials, and components should be reviewed. Focus on the areas where the sterile product is exposed up to and including sealing operations. These critical areas represent the highest risk to the product. The suitability, efficacy, and limitations of disinfecting agents and adequacy of procedures should be reviewed, including the data that establishes the expiry of the disinfection solution. (Reference: Section X.A.3 of FDA's 2004 Aseptic Processing Guidance)
  - For multi-use facilities and non-dedicated equipment, evaluate the adequacy of the changeover procedures and cleaning to prevent cross-contamination between products.

## B. EQUIPMENT

Equipment used in the manufacture of sterile drug products may include the following:

- Production Equipment
- Container/closure processing equipment (e.g. stopper washer, glassware depyrogenation equipment)
- Support system/material system related equipment (e.g. WFI system and related equipment, process gas related equipment)

Specific considerations include:

### (1) Production Equipment

**(a) Aseptic Processing Equipment.** Determine that all equipment that comes in direct contact with product (e.g., filters, transfer lines, holding tanks, stopper bowls, filling line equipment) and sterile components (e.g., stoppers) are sterilized and protected from contamination prior to and during use. Equipment logs or other related information may provide insight into significant maintenance or other problems that may increase exposure of batches to contamination risk.

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

**(c) Capping Equipment (vials).** The vial cap provides the final closure element of a sealed vial. The capping machine folds and crimps the cap (aluminum) over the neck of the stoppered vial. The cap on the vial protects the stopper from external damage, while firmly holding the stopper

in the fully seated, sealed position. Evaluate the established processing settings (crimp angles, pressures), and preventative maintenance schedules of the capping machine. Air supply quality to the capping units should also be evaluated.

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

**(e) Sterilizers.** The inspection should cover the Installation and Operation Qualification of equipment and the Performance Qualification of the process (IQ, OQ and PQ), and operation, calibration and preventative maintenance of representative types of equipment used to sterilize finished dosage forms, filling equipment, containers, closures, etc. Such equipment includes autoclaves, dry heat ovens, dry heat tunnels, steam-in-place (SIP) equipment and chemical sterilization systems (i.e., hydrogen peroxide, peracetic acid). Inspection of sterilizers should include physical examination of the equipment. Review the engineering specifications which may be described in the equipment's DQ (Design Qualification). DQ is performed prior to the IQ (Installation Qualification) and OQ (Operational Qualification), and verify that the sterilizer is maintained, calibrated and drained properly and that it has appropriate measuring devices (temperature sensors, pressure gauges, etc.).

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

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

Reference:

- PDA Technical Report No. 1 Revised 2007 Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control;
- ISO 17665 *Moist Heat Sterilization*.

**(f) Lyophilizer.** Because partially sealed vials are used in the lyophilization process, sterile product is exposed to the environment from the time of filling until the vials are fully stoppered in the lyophilization chamber at the end of the cycle. The inspection should verify that partially

sealed vials are transported and loaded into the lyophilizers under Class 100 (ISO 5) protection. Investigators should observe the transport of vials and loading of lyophilizers.

Other key equipment areas to cover include: validation of the sterilization of the lyophilization chamber between uses, current sterilization controls, leak testing of the chamber, integrity testing of air/gas filters, and calibration of temperature and pressure controllers.

Reference: FDA's *Guide to Inspections of Lyophilization of Parenterals*.

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

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

Reference:

- Appendix 1 of *FDA's 2004 Aseptic Processing Guidance*;
- *PDA Technical Report 51 (2010) Biological Indicators for Gas and Vapor Phase Decontamination Processes: Specifications, Manufacture, Control and Use provides general principles to be considered in decontamination by BI.*

**(h) Restricted Access Barrier System (RABS).** In general, a RABS is a fill-finish line in a rigid wall enclosure that provides full physical separation of the filling line from operators. It is important to note that the inside surfaces of the RABS are disinfected with a sporicidal agent<sup>2</sup>, but this is not accomplished using the automated decontamination cycles employed for isolators. This requires firms to carefully supervise disinfection procedures and assure ongoing effectiveness of the disinfection program. Operators use glove ports, half suits or automation to access areas within the enclosure during filling. There are 2 types of RABS, "open" and "closed" RABS. The doors to a "closed" RABS are never opened during an operation. While an "open" RABS is designed to operate with doors closed at all times, on rare pre-defined circumstances

<sup>2</sup> Robust disinfection of all non-product contact surfaces within the RABS should be performed with a suitable sporicidal agent before batch manufacture. Product contact equipment should be subject to sterilization.



the doors of the enclosure can be opened to perform certain interventions. If doors are routinely opened during a filling operation, the system is not considered a RABS because it no longer restricts access to the critical areas. Typically, the cleanroom surrounding the RABS is controlled as a Class 10,000 (ISO 7) area and operators are fully gowned.

Reference: *Restricted Access Barrier Systems (RABS) for Aseptic Processing*; ISPE; August 16 2005.

When inspecting a RABS:

- Determine that the gloves and gauntlets attached to the glove ports are sterile when installed. After installation, the gloves should be disinfected or changed at appropriate intervals to minimize the risk of contamination.
- Verify there is a well defined written procedure that describes what is done when an open-door intervention is performed. All open-door interventions should be documented and described in batch records, and followed by disinfection.
- RABS entry is often accompanied by an appropriate line clearance, which should be clearly documented in batch records.
- Determine that all fluid pathways and product contact parts such as stopper bowl, feed and placement systems are sterilized prior to the filling of each batch.
- Observe how sterile components and supplies are transferred to the RABS. Verify that the transfer system prevents exposure of sterile surfaces to less clean environments.
- Verify that non-product contact surfaces within the RABS undergo thorough disinfection with a sporicidal agent before each batch. The effectiveness of the overall disinfection program should be validated and routinely evaluated by the environmental monitoring program.

**(i) Blow-fill-seal (BFS) Technology.** BFS is an automated aseptic filling process in which containers are formed, filled and sealed in a continuous operation. BFS systems can reduce the risk of product contamination by reducing operator interventions. The systems are typically used for filling sterile ophthalmic and respiratory care products. See Appendix 2 of FDA's 2004 Aseptic Processing Guidance for information about BFS systems. It should be noted that the inner surfaces of the containers can be exposed to the surrounding environment during the formation and molding steps prior to filling. The sterile product can also be exposed to the environment during the filling and sealing steps of the BFS process. Therefore, the air quality should meet the microbiological level established for Class 100 (ISO 5) should be supplied to where the sterile product or its containers are exposed during the BFS process. Some of the more advanced BFS equipments that provide enhanced protection for the sterile product operation can be located in a Class 100,000 (ISO 8) area. Otherwise, a Class 10,000 (ISO 7) area is appropriate. Research has demonstrated a direct relationship between the number of contaminated units and the level of microbial contamination in the air surrounding the machine (see Reference #20). Typically, the product supply line and sterilizing product filters are steam sterilized-in-place (SIP).

When inspecting BFS:

- Verify that HEPA-filtered or sterile air is used during steps where sterile product or materials are exposed (e.g., parison formation, container molding, and filling steps).
- Evaluate the monitoring and preventative maintenance programs to determine the integrity of the utilities (cooling water, heating, etc.) associated with the BFS machine is routinely checked. Leaks in the molds or utility connections at the molds can contaminate the sterile product or containers.
- Review the SIP system used to sterilize the product line. Determine the sterilization cycle has been validated and the condensate properly drains from the line. The line should also be protected between sterilization and use.
- Verify that personnel who enter the classified environment surrounding the BFS machine are properly gowned and trained.
- If possible, observe equipment setup and any difficulties that can lead to contamination risks.

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

**(j) Reactor, Centrifuge, Dryer, Mill.** This type of equipment can be used to aseptically manufacture sterile bulk Active Pharmaceutical Ingredients (APIs). The equipment and all transfer piping must be sterilized prior to processing. This is typically done with sterilize-in-place (SIP) systems which use clean steam or a chemical sterilant. Review the validation, cycle controls and the routine monitoring of the SIP system. The equipment and all transfer piping must remain integral (no fluid or air leaks) and sterile throughout the entire manufacturing process. Determine how the firm verifies the integrity of the equipment train throughout the process. If a piece of equipment is opened in the process (e.g. adding seed crystals), verify the area surrounding the open operation is robustly protected from contamination risks with a Class 100 (ISO 5) air system as well as implementing a carefully designed aseptic operation.

Reference: FDA's *Guide to Inspections of Sterile Drug Substance Manufacturers*.

## **(2) Container/Closure Processing Equipment**

Depyrogenation equipment may include a dry heat oven and/or depyrogenation tunnel. Depyrogenation of stoppers can also be accomplished by dilution via a washing process. The final rinse of the washing process uses Water for Injection (WFI). For more information, see FDA's Aseptic Processing Guidance, Section VI.B, Containers/Closures.

## **(3) Support Utilities**

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

**(b) HVAC.** Refer to Section IV of FDA's 2004 Aseptic Processing Guidance on qualification and maintenance of the HVAC system.

(c) **Process Gases.** Gases that are in contact with the drug product or components in drug manufacturing operations are referred to as process gases. Gases used in aseptic operations, or downstream of sterilization, must be filtered through a sterilizing grade filter to maintain asepsis. The integrity testing of these filters (typically hydrophobic) should be evaluated. The system used in the generation of the process gas(es) should also be evaluated including preventive maintenance (PM) schedules, monitoring (including temperature, pressure, and humidity), and sampling. See also under Materials System.

### 3.7 MATERIALS SYSTEM

Compliance Program 7356.002 lists the areas to cover when inspecting the Materials System. The areas are applicable to sterile drug products and should be covered if this system is selected. In sterile operations, the quality attributes of each of the materials (ingredients, WFI, containers, closures) have a bearing on the critical attributes of the finished product. Review the firm's procedures for receipt, handling, sampling, testing, approval and storage of manufacturing materials to verify their fitness for use. Emphasis should be placed on incoming materials that are represented to be sterile and / or pyrogen free.

Areas of special concern for sterile drug products include:

(1) **Water Systems.** Water for Injection (WFI) is an ingredient in many sterile drugs, including injectable products and sterile ophthalmic products. It is also used in depyrogenation (or endotoxin removal) of equipment and stoppers and in cleaning operations. The quality of the water, and its endotoxin levels and controls, used in the upstream process should also be evaluated in order to ensure the removal of bacterial endotoxin to the appropriate level downstream. Purified water can be used for some sterile non-injectable solutions.

- Observe and understand elements of the generation and distribution systems.
- Evaluate the water system "As Built" diagrams" and inspect for leaks, pipe slopes (via the isometric diagrams and verification of the degree of the slopes), so called "dead legs", and non-sanitary fittings in the distribution system.
- Evaluate how microbial alert and action levels are established.
- Evaluate sampling sites, procedures, frequencies and tests performed.
- Review procedures for preventative maintenance and calibration of critical instruments, including scheduling and equipment update procedures.
- Review raw data to verify that all of the above is completed per established procedure.
- Review and observe routine monitoring (in-line TOC and conductivity) of water system.
- Review trend data for chemistry, microbiological and endotoxin tests.
- Review investigation of results that are at or over alert and action levels.

Reference: FDA's *Guide to Inspections of High Purity Water Systems*.

(2) **Process Gas.** Process gas and related equipment controls may be covered in conjunction with the Facilities and Equipment System. Specific considerations include controls over final filtration of the

processed gas and filter integrity testing. Gas used as a component in a finished product may include the Nitrogen gas overlay for Oxygen sensitive products.

**(3) Pre-washed / Ready to Sterilize Closures.** The CGMP regulation (21 CFR 211.94(c)) states that, where indicated, containers and closures must be processed to remove pyrogenic substances. Many manufacturers of small volume parenterals purchase stoppers that are ready-to-sterilize, (i.e., they are pyrogen-free). No washing or depyrogenation is done by the dosage form manufacturers but these firms are still responsible for assuring the stoppers are of acceptable quality for use in manufacturing. The pyrogen requirements should be included in specifications for the stoppers and, if the manufacturer does not conduct testing of each incoming lots for pyrogen/endotoxin, they should establish the reliability of the supplier's test results by qualification of the vendor, followed by periodic testing.

**(4) Microbiological and Endotoxin Testing of Component, Container and Closure.** 21 CFR 211.84(d) specifies that each lot of component, container or closure that is liable to microbial contamination which is objectionable in view of its intended use shall be subjected to microbiological tests before use. Evaluate the firm's system for determining if microbiological or endotoxin testing is required and the rationale for setting acceptance criteria. Review test data to verify that the materials meet test criteria and, if not, verify that investigations were conducted to determine the cause and corrective actions were implemented.

**(5) Verification of Container and Closures.** The physical and chemical characteristics of containers and closures can be critical to the sterility and stability of the finished product. Many containers and closures look alike (color and dimensions), but are made of different materials or have a different surface treatment such as silicone on stoppers and ammonium sulfate on Type I glass. Evaluate the firm's procedures for assuring containers and closure consistently meet appropriate specifications. Determine what tests and examinations are done to verify the containers and closures are made of the correct materials with the correct dimensions (critical to ensuring continuing container-closure integrity) and are free of critical defects.

**(6) Container / Closure Integrity.** The integrity of the container / closure system is critical to assuring that all units of drug products remain sterile through shipment, storage and use. Leaking containers or closures lead to product contamination.

Reference: FDA's 1994 *Guidance for Industry for the Submission of Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

Evaluate the tests and studies performed to demonstrate the integrity of container / closure systems for all sterile drugs, including:

- Verify that all incoming container-closure components meet specifications, including all appropriate dimensions.
- Determine studies adequately simulate the stress conditions of the sterilization process, handling and storage.
- Verify that the units tested in validation are appropriate (e.g., for terminally sterilized drug product, the units selected should be exposed to the maximum sterilization cycles using the production process).

- Sensitivity of the test is specified.
- Container-closure integrity is demonstrated during validation and as part of the stability program (in lieu of sterility testing), over the shelf life of the product.

### 3.8 PRODUCTION SYSTEM

Compliance Program 7356.002 lists areas to cover when inspecting the Production System. The listed areas are applicable to sterile drug products and should be covered during inspections.

Production practices and conditions can have a direct and significant adverse impact on drug sterility assurance. The Production System, as well as the Quality System, should be included in all Full Inspections. Coverage of critical elements, which are typically defined by the firm of the Production System, should be part of all inspections (full and abbreviated) of aseptically processed sterile drug manufacturers.

The risk of contamination posed by an operation depends greatly on the design of the overall manufacturing operation. Observation of manufacturing is a critical part of evaluating the adequacy of an aseptic processing operation. The following should be carefully observed.

- adequacy of aseptic technique [See section V of FDA aseptic processing guidance]
- personnel behavior and practices in the cleanroom [See section V of FDA aseptic processing guidance]
- movement of people and materials before and during the aseptic operation
- robustness of production process design (e.g., process performance, validation, impact of equipment configuration on ergonomics of aseptic manipulations) [See section IV of FDA aseptic processing guidance]
- disinfection practices [See section X.A.3 of FDA aseptic processing guidance]

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

- Set-up of filling lines, especially difficult to assemble lines (e.g. powder filling lines), and lines that require multiple aseptic assemblies or do not employ SIP of the product pathway.
- Cleaning and disinfection of the line and room to ensure all difficult to access surfaces are consistently and properly cleaned and disinfected.
- Protection of critical contact surfaces to ensure their sterility throughout operations and post sterilizations.
- Aseptic technique and cleanroom behavior during operations, including handling of equipment jams and stoppages.
- Personnel flow in relation to microbial control of the environment.
- Material flow (e.g., whether materials are moved from a lesser controlled area to a cleaner area without disinfection), including number of staff and their activities in the aseptic filling room.
- Filling operations, especially personnel gowning technique, gown integrity, strict adherence to SOPs), the nature and frequency of interventions (interventions are also performed during the media fill simulations), and overall condition of the critical filling area.
- Atypical interventions associated with unplanned events (e.g., operator attempts to change the filling pump during operations).

- Extra manipulations during filling operations for assembly of sterile filtration apparatus that is not SIP sterilized.
- Handling (transfer, storage, loading) of partially stoppered vials in lyophilization processes. Note that for lyophilized products, vials of sterile products are stoppered but not fully sealed until the lyophilization process is completed. The sterile product is exposed to the environment during filling, half-stoppering, transport, loading of the lyophilizer, and the lyophilization cycle. Complete seating of stoppers typically occurs in the chamber after the cycle is completed. All of these manipulations must be performed under Class 100 conditions.
- Preparation of equipment for sterilization (cleaning, the type of wrapping to ensure protection while still allowing for penetration as part of the validated sterilization cycle with defined loading patterns).
- Environmental monitoring (while the monitoring program is considered a Laboratory System, inspection should include observation of the actual monitoring operations and rationale for sample site locations).
- Proper placement and sealing of stoppers on vials as applicable, and the capping (aluminum crimp) is performed in a protected area under unidirectional flow.
- Production of sterile suspensions and sterile bulk powders (e.g., antibiotics) where sterile filtration of the final bulk is not feasible. These are typically formulated and manufactured under aseptic conditions. This requires the sterilization of large pieces of production equipment (e.g., tanks, reactors, dryers and associated lines) and assurance that these pieces of equipment retain their integrity and remain sterile.

Critical operations that should be covered during an inspection of the Production System include:

**(1) Media fills or process simulations.** Media fills are used to validate aseptic processing operations, including those employing newer technologies, such as isolators, BFS or RABS systems. Media fills representing manually intensive aseptic operations should equal or approach the size and duration of a commercial production lot. In contrast, a process conducted in an isolator is designed to have a lower risk of microbial contamination because of the lack of direct human intervention and can be simulated with a lower number of units as a proportion of the overall operation. All media fills should closely simulate manufacturing operations, incorporating, as appropriate, worst-case activities and conditions as well as operator interventions. FDA's current expectations for media fills are discussed in Section IX.A of the 2004 Aseptic Processing Guidance.

- Verify Media Fills represent actual manufacturing operations by comparing observed operations to those documented in Media Fill batch records.
- Determine if media fills are conducted semi-annually for each processing line. The activities and interventions representative of each shift should be included in the semi-annual media fill program. This may require more than one media fill per line every 6 months, if aseptic processing is performed during more than one shift. With the exception of isolator operations, at least one semi-annual media fill is performed per line per shift. Determine if the aseptic filling of all types of containers are supported by the media fills performed. If a matrix approach is used, evaluate the firm's justification for selecting the worst case container / closure configurations for each line.
- Determine accountability of all filled units (units filled vs. units incubated).

- Verify that all units that were discarded during and after filling have a reasonable and assignable cause for rejection (e.g., rubber stopper missing, aluminum cap missing).
- Determine that cracked and leaking units found after incubation are investigated, counted and all rejected units properly justified (e.g., is there an assignable cause that is reasonable for the rejection?).
- Determine how and who examines units after incubation. If the examination is not performed by a microbiologist, determine if it is overseen by the quality unit and if the operators doing the exam are properly trained by a microbiologist.

Reference:

- FDA's 2004 Aseptic Processing Guidance, Section IX A.
- PDA Technical Report No. 28, revised 2006, Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals.
- PDA Technical Report No. 22, revised 2011, Process Simulation for Aseptically Filled Products.

**(2) Sterile filtration (aseptic processing).**

- Verify filters used in production are identical to those used in validation studies (i.e., those submitted in drug applications)
- Verify that actual operating parameters and allowable extremes are covered in the validation studies.
- Determine that validation of filter sterilization has been performed for all products. Pay special attention to legacy products. These include older products and those for which applications have not been submitted.
- Observe filter integrity testing to verify procedures are followed.
- Review investigations of any integrity test failures.

Reference:

- FDA's 2004 Aseptic Processing Guidance, Section IX.B; and
- PDA Technical Report #26, 2008, *Sterilizing Filtration of Liquids*.

**(3) Sterilization and depyrogenation of containers, closures and processing equipment.**

- Review the validation or revalidation of sterilization and depyrogenation processes used for containers, closures and, in the case of aseptic processing, equipment that comes in contact with the sterile product or sterile components.
- Check if firm verifies that validated parameters (loading patterns, cycle parameters) are met for each load.
- Rubber stoppers that are not purchased pre-sterilized or pre-siliconized may require depyrogenation and siliconization prior to use. As previously noted, depyrogenation may be achieved via a washing dilution process with the use of repeated WFI washing steps. The validation should demonstrate a successful 3-log reduction of bacterial endotoxin. When the firm performs its own siliconization of stoppers, silicon level after wash should be validated to meet the predetermined acceptance criteria.



- Stoppers are sterilized by steam sterilization. Verify that the clean steam used to provide the sterilization is acceptable and has been assayed for endotoxin.
- Review the practices and procedures to determine if a firm needs to revalidate the sterilization and depyrogenation process.
- Review change control procedures.
- Determine if reprocessing is performed.
- Evaluate bioburden level: Evaluate the firm's understanding of process bioburden (e.g., from incoming components/container/closure) and determine if the firm has adequately validated hold time for critical steps. It is important to note that increased bioburden can lead to the degradation of the drug product as well as contributing impurities (including endotoxin) to the drug product. Sampling points (location in process flow) and methods should be evaluated based on product quality risks.

#### **(4) Lyophilization.**

- Review the validation of lyophilization cycles established for selected products.
- Verify the firm confirms all critical cycle parameters are met for each lot.
- Determine environmental monitoring is routinely performed in the areas of loading and unloading of the product from the lyophilizer. In addition, ensure personnel monitoring is conducted on those operators who perform the loading and unloading operations.
- Observe the transport of the partially stoppered vials and the loading of the lyophilization chambers to verify it is done under proper environmental conditions (Class 100) and to verify that proper aseptic techniques are used.

Reference: FDA's *Guide to Inspections of Lyophilization of Parenterals*.

#### **(5) Sealing of vials.**

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

#### **(6) Terminal sterilization.**

- Determine what type of sterilization cycles are used (bioburden based or overkill).
- Review validation / revalidation / or periodic evaluation of terminal sterilization cycles for representative types of products.
- For selected products, verify that the parameters and loading patterns used in production are the same as those used in validation studies.
- Determine the minimum acceptable cycle allowed in the SOP (as opposed to the nominal or routine cycle) and compare that to the validated cycle (using BI) to verify it has been properly qualified.
- Determine how sterilization cycles are documented, monitored and reviewed.

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

**(7) Parametric release of terminally sterilized drug product.** This is defined as a sterility assurance release based on demonstrated control of the sterilization process. It enables a firm to use defined critical process control data, in lieu of the sterility test to fulfill the intent of 21 CFR 211.167(a). It is allowed only for products that are terminally sterilized by heat and it must be identified in the appropriate regulatory filing as the release method. Parametrically released product must have an approved application.

- If encountered during an inspection, verify the parametric release method has been submitted and approved in the appropriate drug application. If the drug is not the subject of an approved application, collect pertinent information and validation data for evaluation by the Center.
- Verify that the conditions described in FDA's Compliance Policy Guide Section 490.200, *Parametric Release – Drug Products Terminally Sterilized by Heat*, are met.

**(8) 100% inspection of injectable products** including: cracks, visible particles and other significant defects.

- Verify the firm has written procedures that define the defects to be removed from the lot and actions to take if the number of critical defects exceeds a pre-determined level.
- Significant defect categories should be identified. Results of inspection of each batch should be compared to established action levels.
- Evaluate the appropriateness of and the rationale or justification for pre-determined action levels.
- Evaluate the firm's investigation into the cause of rejects, including units rejected for cracks and visible particulates (e.g., foreign matter).
- Observe the inspection process.
- Challenge visual/manual inspection rates through observation.
- Evaluate the adequacy of written procedures for visual inspection.
- Evaluate personnel qualification and requalification and equipment qualifications according to established procedures. Evaluate personnel qualification including the use of reference samples for qualification.
  - If a manual system is used, determine if employees are trained and qualified to verify they can recognize and remove defects under actual or simulated production conditions.
  - If an automated or semi-automated system is used, determine the equipment is qualified and the software program or equipment settings have been validated for all types of products being inspected (e.g., clear vials, amber vials, colored solution, suspensions). If the equipment is an automatically controlled computer based system, an assessment of the system and validation is warranted.
- Evaluate the firm's program for sampling and examination of inspected vials and evaluate the effectiveness of inspection and action taken if the reject level is reached.

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

**(9) Personnel (gowning, training, aseptic techniques).** The type of gowns and personal protective equipment (PPE) worn by employees should be appropriate for the areas in which they work. There should be detailed written procedures that describe the gowning requirements for each processing area. Evaluate the following:

- For aseptic processing, determine the gowns (which typically include face masks, hoods, protective goggles, gloves, and boots) are sterilized and made of non-particle shedding material. Ensure that the gowns cover all skin, hair and facial hair.
- Review how the incoming sterile gowns/garb are accepted or rejected for use.
- Evaluate the firm's program for training, testing and qualifying and re-qualifying employees who work in the controlled areas, especially those who set-up and operate aseptic processing lines.
- Evaluate the aseptic techniques of employees by observing aseptic processing operations.
- For selected employees, verify the training, testing, qualifying, and re-qualifying were done as specified in procedures.
- Verify the training is done on a continuing basis.

Reference: FDA's 2004 Aseptic Processing Guidance, Section V.

**(10) Batch records.**

- Review of environmental and personnel monitoring data, as well as other data relating to acceptability of support systems (e.g., HEPA / HVAC, WFI, steam generator) and manufacturing equipment. This review is considered essential to batch release decisions. The batch record should include documentation that assures this type of holistic review is done before the release of a lot for distribution.
- For aseptic processing, verify interventions into critical areas (Class 100/ ISO 5) are documented so they can be reviewed and evaluated by the Quality Unit.
- Review batch records to verify they include complete information for all sterilization processes.

Reference: FDA Aseptic Processing Guidance, Section XII.

**(11) Environmental and personnel monitoring.**

- See section below under "Laboratory Control System".

### 3.9 PACKAGING AND LABELING SYSTEM

Compliance Program 7356.002 lists the areas to cover when inspecting the Packaging and Labeling Control System. All of the areas that are applicable to sterile drug products and should be covered if this system is selected for coverage. Areas of special concern for sterile products include:

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

### 3.10 LABORATORY CONTROL SYSTEM

Compliance Program 7356.002 lists general areas to cover when inspecting laboratories. Inspections of sterile drug manufacturers should also cover microbiology laboratories. Quality control tests (sterility and Limulus Amebocyte Lysate or LAL test) and the collection of environmental and personnel monitoring samples should be observed to verify that acceptable techniques are used and written procedures are followed. The inspection of microbiology laboratory should evaluate the following:

- Sterility testing, including the collection of samples that are representative of the entire lot and processing conditions; adequate control and monitoring of the testing environment; validation of the method for specific products; growth promotion testing of the media; and incubation times and temperature. It is important to note that increasing the number of samples or the number of tests does not greatly increase the probability of detecting contamination if it is present at a very low level in a lot. Reference: FDA's *Guide to Inspections of Microbiology Pharmaceutical Quality Control Laboratories* and FDA's 2004 Aseptic Processing Guidance, Section XI.
- LAL testing, including product specific validation; collection of representative samples of raw materials, components/containers, in-process, and finished product, where appropriate; and adequate laboratory facilities for conducting the tests. Verify the rationale of sample size of endotoxin test relative to the production batch. Reference: *Bacterial endotoxins – Test methodologies, routine monitoring, and alternatives to batch testing*. ANSI/AAMI ST 72:2002/ (R) 2010, Association for the Advancement of Medical Instrumentation.
- Environmental monitoring, which includes: a well defined written program that covers all production shifts and includes air, floors, walls, equipment surfaces, and, in aseptic process

operations, critical surfaces that come in contact with sterile product, containers and closures; establishment of appropriate alert and action levels, use of sampling (contact plates, swabs, active air samplers) and testing methods (media, plate exposure times, incubation times and temperatures) that are designed to detect environmental isolates. Evaluation of the validity of the sampling locations and sampling methods. Reference: FDA 2004 Aseptic Processing Guidance, Section X. Note: environmental monitoring is performed during the processing of all types of sterile drug products, including an appropriate program for terminally sterilized products.

- Personnel monitoring which includes: a routine program for daily/shift monitoring of operators gloves and an appropriate schedule for monitoring gowns; establishment of limits that are based on the contamination risk to the product; and investigations of results that exceed the established levels or demonstrate an adverse trend. Personnel monitoring is important in all sterile product operations, but it is especially critical in aseptic processing, and inspectional emphasis should be risk based, focusing on those operations that require employees to enter the critical areas of the processing line. Reference: FDA's 2004 Aseptic Processing Guidance, Section V.C.
- Efficacy of disinfectants, including assessment of the suitability, efficacy and limitations of the disinfecting agents used in the controlled area, production equipment and laboratories. The firm's assessment typically includes laboratory studies that test the effectiveness of agents on different surface materials. Material coupons are usually used with surface types as found in production. The studies should be done with the same disinfecting agents, contact times (which should be clearly defined in written procedures). It is also important to understand that disinfectants have limitations and most are not effective against every type of microorganism. For this reason, firms should normally use more than one type of disinfectant. Reference: FDA's 2004 Aseptic Processing Guidance, Section X.A.3.
- Identification of microorganisms, including procedures that require identification of organisms found in positive sterility tests, media fills, and environmental monitoring (environmental and personnel) samples as specified by the firm. The program should assure routine identification of microorganisms found in samples are taken in critical areas, surrounding areas and from personnel in the production area. Review the procedures, equipment and controls used in identification activities of the contaminants.
- Microbiological media, including the preparation, sterilization and growth promotion testing of the media used in performing tests (sterility tests, raw material testing, pre-filtration bioburden, environmental monitoring, media fills, etc.). Where appropriate, inactivating agents for disinfectants or product residuals should be added to allow detection of contaminants.
- BIs and biological cultures used in sterilization validation studies should be used and stored under appropriate conditions. Typically, the conditions are described in the literature received with the BI, if supplied by a vendor. The microbial population should be confirmed by testing each lot. Spore counts should be verified prior to use in validation studies. The D-value should be determined for each lot of a BI if it is used in a way not described by the vendor. If used specifically as directed, the D-value supplied by the vendor can be accepted if the reliability of the Certificate of Analysis has been established, but D-value of incoming batches should be periodically verified. Reference: 2004 FDA Aseptic Guidance.

- Microorganisms (e.g., ATCC) are used for growth promotion tests of media. Organisms isolated from environmental monitoring samples can also be used to perform growth promotion test.
- Monitoring, calibration and maintenance programs for microbiology laboratory equipment, such as incubators.
- Training of microbiologists and evaluation of microbiologists or technicians that perform sterility, LAL and environmental monitoring tests.
- Documented investigations into out-of-specification results. Evaluate positive sterility tests and media fill and LAL failures investigations. Also review environmental / personnel monitoring results at alert and action levels to identify and determine the firm's response to the significant incidents or trends. Because of the limited sensitivity of the sterility tests to detect batch contamination, any positive is a serious issue and should be thoroughly investigated by the firm with quality unit oversight and approval. The investigation and followed should be reviewed during inspections to assess the decision making process. An initial positive can be found invalid only if there is clear documented evidence that the microbial growth was unequivocally a laboratory error. Reference: Section XI.C of FDA's 2004 Aseptic Processing Guidance.

21 CFR 211.180(e) requires that records be maintained in such a manner that the data can be used to evaluate adherence to quality standards. The evaluation of data generated by the microbiology lab plays an integral role in establishing the sterility assurance of the finished product. The inspection should determine if the firm generates and reviews testing data and product quality related data (e.g., trend reports) to make timely, informed and science-based decisions to assure an ongoing state of control.

### 3.11 SAMPLING

Samples of sterile drug products should be collected to document suspected contamination, adulteration or misbranding encountered during an inspection. The samples can be physical or documentary. In the event of a for-cause assignment where in-process samples are being requested, collect the samples aseptically at points where such contamination might occur. These samples should be collected by the firm under the observation of the investigator. Great care shall be taken to prevent the possibility of contamination and/or compromising the integrity of the sample for all physical samples of raw materials, in-process samples or finished drug products. Consult the district management and/or Center as well as the servicing laboratory for guidance on sample size and sampling techniques. A production lot with an initial sterility failure result that was invalidated by the firm may be considered a good candidate for sampling.

Physical sample analysis is not necessary to document CGMP deficiencies. Documentary samples may be submitted when the documentation illustrates the deficiencies and to obtain evidence of interstate shipment. Please be aware to collect the appropriate number of sample units in order to accommodate the 702(b) section of the Act.

For finished products requiring sterility testing, collect 48 units of product. For finished products requiring endotoxin testing, collect 20 units of product.

For additional sampling guidance, refer to Investigations Operations Manual (IOM) Chapter 4.

[end Part III]

**PART IV - ANALYTICAL**

In general, samples will be submitted to your District's designated servicing laboratory, except as requested in a special assignment or your supervisor.

**4.1 . ANALYZING LABORATORIES**

For Sterility and Bacterial Endotoxin testing:

<b>Region</b>	<b>Examining Laboratory</b>
NER	NRL
SER	SRL
CER	NRL
PAR	SAN-DO
SWR	DEN-DO

For particulate matter in injectables analysis, contact the ORA Office of Regulatory Science/Medical Products and Tobacco Staff to determine the most appropriate laboratory for this test.

**4.2 ANALYSIS**

Sterility testing methods should be based on current editions of USP <71> Sterility Tests and the Sterility Analytical Manual (SAM). The SAM provides supplemental information to the USP. The SAM has the goal of standardizing the performance of testing for pharmaceutical microbiology in FDA laboratories.

Bacterial endotoxin testing methods should be based on current editions of USP <85> Bacterial Endotoxin Test and the Sterility Analytical Manual (SAM).

Particulate matter testing methods should be based on current editions of USP <78>.

Other microbiological examinations should be based on appropriate sections of USP and the SAM.

[end Part IV]



## PART V - REGULATORY/ADMINISTRATIVE STRATEGY

A recommendation for regulatory action should be submitted by the District Office when a judgment is made that the firm is not operating in a state of control and management of the firm is unwilling or unable to make adequate corrective actions in an appropriate time frame. The therapeutic use of the drug product and the potential adverse effect of the CGMP deviations on the finished product must be considered in determining the appropriate action needed.

When deciding the type of action to recommend, the initial decision should be based on the seriousness of the problem and the most effective way to protect the consumer (i.e., when non-sterile parenterals are found, injunction/seizure, recall would be the action(s) of choice). Instructions in the Regulatory Procedures Manual (RPM) should be followed.

If the nature of the CGMP deviations is determined to pose minimal risks when considered in relation to the intended use of the drug, the primary action should normally be voluntary corrections by the firm. The District should require that all commitments for achieving voluntary compliance by firm management be submitted in writing and contain a time schedule for completion. The District should determine if the schedule is a reasonable time frame and should monitor the progress.

When voluntary action is not accomplished or when the deviations observed pose a serious risk to the consumer, regulatory and / or administrative action should be recommended.

**NOTE:** Regulatory action is independent of the collection of a violative physical sample. The lack of a violative physical sample is not a barrier to pursuing regulatory and/or administrative action providing the CGMP deficiencies have been well documented. Physical samples found to be in compliance likewise are not a barrier to pursuing action under CGMP charges.

The following list of deficiencies represents examples of practices that CDER believes could warrant regulatory and/or administrative action (please note the following is not intended to be an inclusive list):

1. Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals; or a reasonable potential for product contamination, with demonstrated avenues of contamination such as poor aseptic methods, contact with unclean equipment, or airborne contamination.
2. Failure to assure that each batch conforms to label claims or established specifications, such as NDA, ANDA, USP monographs, and the firm's finished product specifications.
3. Distribution of product which does not conform to established specifications.
4. Lack of adequate validation of critical steps in sterilization processes, including sterilization by filtration; sterilization cycles used for drug products; and, for aseptically processed products, sterilization processes used to sterilize components (formulation and/or its ingredients, as well as containers and closures), or to sterilize equipment surfaces that contact sterile product or any elements of the product.
5. Lack of adequate validation of aseptic processing operations (media fills).

6. Failure to appropriately conduct and document investigations of discrepancies and failures of drug products or any of their components to meet specifications, especially inadequate investigations of sterility test failures, media fill failures and repeated or significant environmental or personnel monitoring results that meet or exceed action levels.
7. Facilities and equipment which do not provide adequate protection for aseptically processed product while the sterile product or sterile components are exposed to the environment. This includes both lack of robustness due to poor design, as well as failure to maintain equipment as sterile (e.g., by providing proper barriers as well as assuring adequate sterilization frequency).
8. Failure to assure a robust cleanroom disinfection program. This may include the failure to assure sufficiently detailed cleaning procedures to assure repeatability in cleaning, or failure to demonstrate the suitability and efficacy of the disinfecting agents used for the critical controlled areas and production equipment.
9. Failure of a WFI system to deliver water that consistently meets chemical, microbiological and endotoxin specifications.
10. For aseptic processing, poor employee practices that increase the risk of product contamination.
11. Failure to provide adequate training to employees who work in critical operations, such as operators on aseptic processing lines, operators responsible for initiating and checking sterilization cycles and those who perform the 100% inspection of filled injectable products.
12. Failure to perform adequate 100% inspections of injectable products for particulate matter and other defects.
13. Failure of batch records to include complete information related to the production and control of each batch, including documentation that assures environmental and personnel monitoring data and data related to the support systems, and assure quality unit review of these records prior to approval of a lot for distribution and release. For aseptically processed product, batch documentation includes records of purposeful operator interventions into critical (Class 100 / ISO 5) areas of the line. Operator intervention should be minimized as much as possible to preclude and control contamination.
14. Use of test methodology (sterility test, endotoxin test) that is not adequate or validated.
15. Lack of an adequate environmental monitoring program, that is, one that does not include dynamic monitoring during all production shifts or has not established appropriate alert and action levels and, in the case of aseptic processing, does not include representative critical surfaces that come in contact with sterile product, containers and closures.
16. Lack of an adequate personnel monitoring program for aseptic processing operations. For example, the program does not include daily monitoring of operators' gloves and periodic monitoring of gowns; has not established appropriate limits or does not require investigations and corrective actions when limits are exceeded.

[end Part V]

## PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

### 6.1 REFERENCES

All of the references listed below, with the exception of number 17 through 26, are available on FDA's internet website.

1. Code of Federal Regulations, Title 210 and 211 as revised, including the preamble.
2. *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*; FDA; September 2004.
3. *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*; FDA; November 1994.
4. *Guidance for Industry Process Validation: General Principles and Practices of Process*; FDA; January 2011.
5. *Guide to Inspections of Lyophilization of Parenterals*; FDA; July 1993.
6. *Guide to Inspections of Microbiology Pharmaceutical Quality Control Laboratories*; FDA; July 1993.
7. *Guide to Inspections of High Purity Water Systems*, FDA; July 1993.
8. *Guide to Inspections of Sterile Drug Substance Manufacturers*; FDA; July 1994.
9. *Guide to Inspection of Dosage Form Drug Manufacturers*; FDA; Oct. 1993.
10. *Compliance Policy Guide 7132a.13, Parametric Release – Drug Products Terminally Sterilized by Heat*; FDA.
11. Compliance Program 7356.002, *Drug Manufacturing Inspections*.
12. Compliance Program 7356.002C, *Radioactive Drugs*.
13. Compliance Program 7356.002M, *Inspection of Licensed Biological Therapeutic Drug Products*.
14. *Investigations Operations Manual*
15. *Guide to the International Inspections and Travel*
16. *Regulatory Procedures Manual*
17. *Restricted Access Barrier Systems (RABS) for Aseptic Processing ISPE Definition*; ISPE; August 16 2005.;
18. ISO 17665 *Moist Heat Sterilization*.
19. ISO 14644 *Cleanrooms and Associated Controlled Environments*.
20. ISO 14698 *Cleanrooms and Associated Controlled Environments- Biocontamination Control*.
21. PDA Technical Report No. 1 (Revised 2007) *Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control*.

22. PDA Journal of Pharmaceutical Science & Technology; Vol. 49, No. 6; November – December 1995 *Performance of Blow/Fill/Seal Equipment under Controlled Airborne Microbial Challenge*.
23. PDA Technical Report 51 (2010) *Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specifications, Manufacture, Control and Use*.
24. PDA Technical Report No. 22, revised 2011, *Process Simulation for Aseptically Filled Products*.
25. PDA Technical Report No. 28, revised 2006, *Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals*.
26. PDA Technical Report #26, 2008, *Sterilizing Filtration of Liquids*.
27. Bacterial endotoxins – *Test Methodologies, Routine Monitoring, and Alternatives to Batch Testing*. ANSI/AAMI ST 72:2002/ (R) 2010, Association for the Advancement of Medical Instrumentation.
28. CGMP Q&As. FDA website.
29. Sterility Analytical Manual (SAM); FDA May 2012.

## 6.2 ATTACHMENTS

A “Inspections: Points to Consider” This attachment includes a list of questions intended to be an aid in conducting inspections and obtaining information needed to assess a firm’s operations. This list of questions and/or considerations is not intended to be an all inclusive or an exhaustive list of concerns. They are intended to assist focusing of the inspection and include areas worthy of consideration and evaluation during an inspection. The answers do not have to be reported in the EIR unless they are relevant. The list of questions covers: Moist Heat Sterilization; Dry Heat Sterilization / Depyrogenation; Aseptic Filling; Lyophilization; Isolators; Environmental Monitoring; and Biological Indicators. CDER welcomes feedback and any additional questions to this list.

## 6.3 CONTACTS

### Office of Regulatory Affairs (ORA)

For technical questions concerning inspections contact:

Office of Regulatory Affairs (ORA)  
Office of Medical Products and Tobacco Operations (OMPTO)  
Division of Medical Products and Tobacco Program Operations (DMPTPO)  
Telephone number: 301-796-0358  
FAX number: 301-827-6685

For questions concerning particulate matter in injectables analysis and appropriate testing laboratory contact:

Office of Regulatory Affairs (ORA)  
Office of Regulatory Science (ORS)  
Medical Products and Tobacco Scientific Staff (MPTSS)

Bruce Harris  
Telephone number: 301-796-3030  
E-mail: [Bruce.Harris@fda.hhs.gov](mailto:Bruce.Harris@fda.hhs.gov)

For questions concerning microbiological analysis, sterility issues and related sampling concerns contact:

Office of Regulatory Affairs (ORA)  
Office of Regulatory Science (ORS)  
Medical Products and Tobacco Scientific Staff (MPTSS)  
Norma Duran  
Telephone number: 301-796-6133  
E-mail: [norma.duran@fda.hhs.gov](mailto:norma.duran@fda.hhs.gov)

### **Center for Drug Evaluation and Research (CDER)**

For questions relating to product quality, the application of CGMPs and sterility assurance issued contact:

Office of Manufacturing and Product Quality, Office of Compliance  
Telephone: 301-796-3120  
FAX: 301-847-8742

CDER maintains a list of contacts to help answer CGMP regulatory, technical and program questions. The subject contact list is at <http://www.fda.gov/cder/dmpq/subjcontacts.htm>

[end Part VI]

## **PART VII - CENTER RESPONSIBILITIES**

### **A. COMPLIANCE**

The Office of Manufacturing & Product Quality will evaluate the operations under this Compliance Program. Reports of these evaluations will be shared with the ORA Headquarters offices, field offices and CDER headquarters offices.

The Center reviews enforcement recommendations and provides the agency's technical decisions in coordination with District Offices and Office of Chief Counsel

### **B. DRUG SHORTAGES**

If a violative conditions are identified that may result in a shortage, field staff should notify CDER drug shortage staff at [DrugShortages@CDER.fda.gov](mailto:DrugShortages@CDER.fda.gov) and ensure the company also contacts this staff. This notification should occur as soon as the District becomes aware of a possible shortage or through communication with the firm.

CGMPs are a preventive system intended to preclude to the occurrence of critical product defects and loss of assurance of quality. A warning letter is an advisory action meant to notify a manufacturer that significant violative conditions compromising the assurance of quality, safety, and/or efficacy were observed and must be promptly corrected by an appropriate and timely action plan. In situations where the firm's corrective actions may reduce the supply of medically necessary products, the agency will work closely with the firm to assure the medically necessary drugs remain available and the CGMP deficiencies are corrected in a timely manner.

[end Part VII]

## Inspections: Points to Consider

Below is an extensive list of questions provided as an aid in conducting inspections and obtaining information needed to assess a firm's operations.

- This list of questions and/or considerations is not intended to be an all inclusive or an exhaustive list of concerns. They are intended to assist focusing of the inspection and include areas worthy of consideration and evaluation during an inspection.
- The answers *do not* have to be reported in the EIR unless they are relevant.

### TOPICS:

[Moist Heat Sterilization](#)

[Dry Heat Sterilization / Depyrogenation](#)

[Aseptic Filling](#)

[Lyophilization](#)

[Isolator Barrier Technology](#)

[Environmental Monitoring \(Non-viable\)](#)

[Environmental and Personnel Monitoring – Microbiology](#)

[Biological Indicators.](#)

CDER welcomes feedback and any additional questions to this list.

## MOIST HEAT STERILIZATION

*Reference: PDA Technical Report No. 1 Revised 2007 Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control; and*

### General.

1. Who is the manufacturer of the steam sterilizer (autoclave)?
2. What is the model number, age, and internal volume of the autoclave?
3. What is the sterilizing agent? (e.g., steam, air over pressure, superheated water, gamma irradiation)?
4. If jacketed, what pressure/temperature is maintained in the jacket as opposed to the chamber?
5. What types of vent filters are used and how often are they integrity tested?
6. Are vent filters hydrophobic? Are the vent filter housings heated to prevent condensation?
7. Are cycles controlled manually or automatically?
8. What type of monitoring and controlling sensors are used (e.g., mercury-in-glass thermometer, thermocouple, RTD, pressure gauge)?
9. How are these sensors calibrated? Are the standards NIST traceable (or traceable to a National standards for foreign firms), where appropriate?
10. Is the autoclave equipped with a steam spreader (more than one steam entry line would be considered in this category)?
11. If more than one autoclave is used by the firm, what is the system's capacity for steam production in relation to all autoclaves being in operation at the same time?

12. What are the sterilization cycle parameters? (Compare Master Process Record / SOP specifications against processing records completed for selected drug products)
13. What are the firm's specifications and observed parameters for:
  - Time
  - Temperature
  - Pressure (psi, in. Hg)
14. Where is the cycle controller sensor located?
15. How are each of the sterilization (#13) parameters monitored? Are the come-up times for chamber temperature during sterilization reproducible when compared to the come-up time achieved in validation studies?
16. Is the slowest to heat spot ("cold spot") in each load monitored during each autoclave cycle?
17. Have any changes in the steam sterilization system occurred since the last EI? Have these changes been evaluated for the need for re-validation?
18. Is clean steam being used (control of bacterial endotoxin)?

**Validation.**

19. Does the firm have written procedures for validation that include
  - Design Objectives
  - Installation qualification (IQ) of equipment
  - Operational qualification (OQ) of equipment
  - Performance qualification (PQ) with product (maximum and minimum load submitted in the application, and any changes after)
  - Description of circumstances requiring revalidation of the system
  - Procedures for revalidation
20. Does validation documentation include the following?
  - A. Empty chamber / loaded chamber heat distribution studies:
    - Number of runs?
    - Was cold spot determined?
    - Allowable variation?
    - Actual variation found?
    - What is the worst-case load?
  - B. Heat penetration studies
    - For each type of loading pattern/for each container size utilized?



- Number of runs per pattern?
  - Was the "cold spot" determined for each pattern?
  - Is the established load configuration submitted in the application followed and/or reportable changes submitted as appropriate?
21. What type of temperature measurement system was used? Does it provide a separate printed reading for each thermocouple?
22. What type of temperature sensors were used, and were they calibrated before and after each run?
23. If biological indicators were used during validation runs:
- Type of indicator (spore strip, inoculated product, ampule)
  - Source of indicator
  - Microorganism used, including concentration and D value
  - Were BIs used in an "end point" or "count reductions" mode? If any positive BIs were found (when not expected), what was the firm's response?
23. In the event a heat distribution or penetration variance was disclosed during the studies, how did the firm correct or allow for it?
24. Has the firm determined lag times for all container sizes/mass, product viscosities, etc. and adjusted their cycles accordingly?

## **DRY HEAT STERILIZATION / DEPYROGENATION**

Dry heat sterilizers are used, primarily, to sterilize and depyrogenate glass containers for injectable drug products. Both dry heat ovens and dry heat tunnels are used. An oven is a batch process and, at the end of the cycle, the sterile vials are manually removed from the oven, transported and then manually loaded onto the filling line. A dry heat tunnel uses a continuous, integrated process. In a tunnel, the vials move on a belt from the wash processing through a heating zone where the vials are sterilized and depyrogenated to a cooling zone and then directly into the Class 100 area of a filling line. Typically, firms validate the depyrogenation of the glassware rather than the sterilization cycle. This is based on the fact that it is generally more difficult to remove or denature pyrogenic substances than microorganisms. Components that have undergone heat depyrogenation are rendered sterile.

### **General.**

25. Determine what types of dry heat sterilizers are used (ovens, tunnels)?
26. Determine the location of the heat source. The heating element/device that generates the depyrogenation temperature can affect the HEPA filters and their ability to provide the desired filtration for non-viable particles. For example, the high temperatures create expansion and contraction of the HEPA filters and filter housing, which can compromise the integrity and functionality of the HEPA filters.
27. How is the heat distributed in the oven or tunnel (fan or convection)?

28. Where are the HEPA filters located in the oven or tunnel? What zones in a tunnel are supplied with HEPA filtered air (supply, heating, cooling zones)? Does the cool down section of the tunnel provide a Class 100 conditions to ensure the sterility of the containers are maintained? What zones are controlled as Class 100 areas?
29. Due to thermal dynamics (high temperature of >360 degree C leads to the expansion and contraction of the filter housing), the HEPA filter normally undergoes integrity testing every 6 months. However, depending on the amount of usage of the depyrogenation tunnel and data obtained from particle monitoring in the vicinity outside the heat tunnel, integrity testings may need to be conducted on a more frequent basis. How does the firm assure integrity of the HEPA filters? How often are HEPA filters changed?
30. Are non-viable particle counts taken in hot air tunnel? Non-viable particle measurement for the Class 100/ ISO-5 zone of the depyrogenation tunnel are not done during routine operation because of high temperature. However, periodic measurement of non-viable in ISO 5 area should be verified and they are normally measured prior to and subsequent to the manufacture of a batch/campaign and at ambient temperature.
31. Are the sterilization / depyrogenation cycles controlled manual or automatically?
32. What type of monitoring and controlling sensors are used (e.g., thermocouple, RTD, pressure gauge, belt speed indicators)? How often are they calibrated?

**Parameters.**

33. What are the sterilization / depyrogenation cycle parameters or equipment settings? Compare master production record / SOP specifications and processing records for specific representative products.
34. What are the firm's specifications for time, temperature, belt speed, and pressures if applicable?
35. What are the critical parameters? How were they established? How does the firm assure the critical parameters are met for each lot or cycle?
36. Where are the sensors for the cycle controllers located?
37. How are each of the above parameters monitored? Are any of the parameters not monitored? Are the critical parameters alarmed in continuous systems, such as those used in tunnels? What is done when there is an alarm?
38. How does the firm assure that all critical parameters are met for each cycle in an oven or for the continuous run of the tunnel?
39. Do dry heat tunnels have alarms to alert operators if critical parameters (heat, belt speed, pressure) are not met? Are the alarms documented? Did the conditions that caused the alarm require the implementation of change controls and did they impact the validated process?

40. Have any changes in the dry heat sterilization / depyrogenation system occurred since the last inspection? Have these changes been evaluated for the need for revalidation?

**Validation.**

41. Does the firm have written procedures for qualifying the dry heat sterilizers that include:
- Design Objectives
  - Installation qualification of equipment
  - Operational qualification of equipment
  - Performance qualification with product
  - Description of circumstances requiring re-validation and procedures
42. Does validation documentation include heat distribution / penetration studies?
- What is the firm's allowable temperature variation and the actual variation found in production?
  - What type of temperature measurement system was used?
  - Was calibration performed before and after the validation?
  - If dry heat sterilizer is an oven, was the slowest to heat area determined?
43. How was the depyrogenation cycle validated?
- Was a known amount of endotoxin added to vials?
  - Was the endotoxin allowed to dry on the vials?
  - Was validation conducted with recovery tests to assure the spiked endotoxin can be recovered? Were the vials challenged with enough endotoxin to allow calculation of a 3-log reduction?
  - What cycle or equipment settings were used in the validation runs?
  - Was a 3 log reduction of endotoxin achieved?
44. Are the depyrogenation cycles for all vials validated or does the firm use a matrix approach? If a matrix approach (vial sizes/mass) is used, what criteria are used to select the worst case challenges to the system? Are all vials types and sizes bracketed?
45. Have the dry heat sterilizer cycles or equipment settings changed since the validation studies were completed? Compare validation studies, current SOPs and processing records for recent batches.

**ASEPTIC FILLING**

46. When observing personnel during production, do operators practice proper cleanroom behaviors as specified in established cleanroom SOPs?
47. Can you observe the aseptic filling processes without going into the clean room (i.e., through window or TV monitor)?

- A. If yes, watch / observe the aseptic filling processes from preparation of bulk liquid product to filling and sealing of final dosage form, including the environmental monitoring performed in critical areas during actual production.
- B. If not, consider observing the aseptic filling inside the clean room, for example, via a Class 10,000 (ISO-7) area. Prior to entry, consult the District.
- Do personnel enter and perform interventions at the critical Class 100 (ISO 5) areas of the filling lines? If so, how are such entries recorded?
  - How is this done (full body entry, hands only)?
  - Why?
  - Is this done routinely or infrequently?
  - Are proper aseptic techniques used? [Reference: FDA 2004 Aseptic Processing Guidance, Section V.A.]
  - Do hands or arms go over open vials for sterile components? If yes, are the vials discarded?
48. Does the firm have written procedures describing aseptic filling of drug products? Does it include discussions of proper aseptic techniques and acceptable techniques for performing interventions into the Class 100 areas?
49. Review trend reports of the non-viable, viable and personnel monitoring data.
- Have any trends been identified by the firm? If yes, what is done?
  - Are investigations done of out of limit results?

### **Aseptic Filling Validation.**

*Reference: FDA's 2004 Aseptic Processing Guidance, Section IX*

50. How does the process used for media fill compare to the aseptic filling of commercial drug products? Does the firm accurately evaluate the production operation on a routine basis (changes over time) against the media fill design? Does the firm have detailed procedures that describe the media fill process, including frequency, challenge conditions, personnel participation, container / closures, interventions, duration of fill, reconciliation of vials, acceptance criteria, incubation, examination after incubation, actions to take if positive growth is found, etc?
51. Request a summary of all media fills conducted since last inspection, including lot identification, fill dates, production lines, number of units filled, number of units incubated, number of vials with no growth, number of vials with positive growth, microbial identification for any containers with growth, disposition of media fill units, etc.
- Have media fills been done at the frequency described in the procedure?
  - Have any media fills showed positive growth?
  - Have any media fills failed to meet acceptance criteria?

52. Are procedures followed when positive growth is found in media filled vials? Are investigations conducted of all positive growth found in media filled vials? What is done when a media fill fails to meet acceptance criteria? Review investigations of any positive growth.
53. Are media fills performed on all shifts (e.g., representative of shift operations in a campaign)? Do media fills include shift changes and breaks that occur during routine production?
54. When can media fills be aborted or units not incubated? Would production lots be rejected if the same conditions existed during filling?
55. Are all personnel included in the media fill program? Does this include set up personnel and mechanics who work on the aseptic filling lines? What system does the firm have for assuring all personnel are included?
56. If end-line filters are used in actual manufacture, are they also used during media fills?
57. What size vials or ampules are used for media fills? Evaluate justification for selecting worst case challenge if firm does not perform media fills using all the container / closure configurations filled on the line.
58. Are vials inverted before incubation to assure media touches all inner surfaces?
59. How does the firm conduct media fills for products that are filled into amber or opaque containers?
60. How does the firm assure that all integral vials are incubated? How does the firm handle filled vials removed during the run because of interventions?
61. Do media fills include interventions that occur during routine production? Are there written procedures specifying removal of media fill units (type of intervention and number of units removed) corresponding to the practice of a routine production run? Did you observe any interventions during the filling of routine production lots that are not included in media fills?
62. Does the duration of a media fill approximate the duration of a routine production lot? If not, evaluate firm's justification for running shorter media fills?
63. What is the microbial growth medium?
64. Are growth promotion studies performed on each type of medium used?
65. Are growth promotion studies conducted every time a media fill is done?
66. When are the growth promotion studies performed (before/after filling; after incubation; etc.)?
67. What organisms are used to perform the growth promotion tests? Are any environmental organisms used?
68. What temperatures and incubation times are used to incubate media filled vials?

69. Are microorganisms from positive vials identified to genus and species? Are such microorganisms correlated to those found during environmental monitoring?
70. Is an investigation done when cracked vials are found after incubation begins?
71. When and where are the media filled vials examined?
72. Who performs the examination of media filled vials? If production employees perform the examination, have they been trained to recognize all types of microbial growth. Is a microbiologist present when the examination is done?
73. What incubators are used to incubate media filled vials? How is the temperature controlled and monitored? Have tests been done to determine if the temperature is uniform throughout the incubator?

### **LYOPHILIZATION (FREEZE-DRYING)**

*Reference: Guide to Inspections of Lyophilization of Parenterals; FDA; July 1993*

#### **General.**

74. Who is the manufacturer of the lyophilizer?
75. Describe the heating and cooling systems used in the lyophilizer; the vacuum system; gas that is used to break the vacuum and whether it is sterile; and the temperature controlling system.
76. How are the vials transported from the filling line to the lyophilizer? How are Class 100 (ISO 5) conditions maintained during transport, loading, and unloading of the lyophilizer?
77. Are the loading and unloading of the vials automated or manual?
78. How is the sealing of vials (final seating of stoppers) performed?
79. If the stoppering is performed automatically in the chamber at the end of the cycle, is it under vacuum? If not under vacuum, what gas is used and how is it sterilized?
80. If the vials are stoppered outside of the chamber, how is the lyophilized product protected from contamination during transport to the stoppering station and during the stoppering operation?
81. Describe the chamber clean-up procedures between batches of the same product and between different products (including sterilant / cleaning agents used, monitoring for sterilant residue where appropriate, and exposure cycle).
82. Past history has shown that the lyophilizer condenser can be a source of contamination and an assessment of the lyophilization process should include an inspection of the condenser. How is lyophilization cycle monitored/ documented and reviewed?

**Lyophilization Validation – Sterilization of Chamber.**

81. How is the lyophilization chamber sterilized? How are all surfaces, such as all surfaces of moving shelves, exposed to steam?
82. When is the lyophilization chamber sterilized? What is explanation / justification if it is not done between each batch?
83. How are sterilization cycles controlled (manual, programmed)? How are cycles monitored during production?
84. Has the sterilization of the lyophilization chamber been validated? Have the slowest to heat surfaces in the chamber been determined and challenged in the validation runs?
85. Review current procedures and sterilization records for production lots. Are the cycle parameters the same as those used during validation? Do production cycles meet the validated cycle parameters?

**Lyophilization Validation – Aseptic Handling.**

86. Is the aseptic handling of lyophilized products validated by media fills?
87. In the aseptic process, is lyophilization simulation performed during media fill?
88. Is the maximum amount of time the vials are held prior to lyophilization simulated during media fills? If vials are not sealed in lyophilization chamber, is the maximum hold time prior to stoppering simulated in media fills?
89. During validation, what level of vacuum is pulled on the lyophilization chamber?
90. How long do media fill vials remain in the lyophilization chamber under vacuum? How does this compare to commercial lots?
91. Does the process simulation result in freezing of the media? Note that this process simulation should not include freezing of the media.
92. Is environmental monitoring performed during loading of the lyophilizer both during production and as well as during validation?
93. Does the firm have data on growth promotion of the media? Are growth promotion tests done on vials after incubation is completed?
94. Is environmental monitoring performed during unloading of the chamber during production as well as during media fill validation?
95. What is used to break the vacuum during media fills (nitrogen, air, other gas)?

**Lyophilization Validation – Process.**

98. Has the firm validated the lyophilization cycle (e.g., time, rate of heat input, temperatures, eutectic melting point) for each product? Review validation records for selected drug products with different physical and chemical characteristics.
99. Review lyophilization production records for the same products. Are the cycle parameters and observed results within the validated cycles?
100. What are the firm's criteria for acceptable vs. unacceptable runs, including general appearance, cake appearance, meltback, reconstitution time, moisture, etc.?
101. Has the firm performed equipment qualification, preventative maintenance, critical instrument calibration, and cleaning validation?

Lyophilization of sterile API: The aseptic process may include either a manual or automated transferring process, or a combination of both, to transfer the lyophilized API out of the lyophilizer and into an SIP holding vessel or transfer tank. It is equally important to observe and assess the manual operations of the aseptic lyophilization process and assure that similar operations are performed during the media fill processing steps for the API.

**ISOLATOR BARRIER TECHNOLOGY**

*Reference: Appendix 1 of FDA's 2004 Aseptic Processing Guidance*

**NOTE:** Methods (e.g., hydrogen peroxide, peracetic acid) used to decontaminate isolator barriers are capable of rendering surfaces free of viable organisms, but lack the capabilities of steam sterilization. While these agents do not effectively penetrate obstructed or protected surfaces, validated systems are highly effective at assuring contamination-free internal isolator surfaces.

102. Determine:
  - Model of isolator or barrier, and materials of construction
  - Type of isolator (open or closed)?
  - Airflow (turbulent, unidirectional)?
  - Classification of surrounding room environment
  - Number and location of gloves or half-suits
  - Attire worn by operators (e.g., are sterile gloves worn under isolator gloves?)
  - Operating parameters (pressures, air velocities, temperature, humidity)
103. Is a written maintenance program in place which requires routine documented checks or tests of gloves, half-suits, door seals, etc. for integrity? What type of tests/checks are done and how frequently?



104. Do written procedures specify glove replacement frequency? If so, what is the frequency and is the SOP followed?
105. Does the isolator maintain continuous positive pressure and at sufficient levels?
106. How are materials transferred into and out of the isolator? How robust are the transfer mechanisms?
107. Are the equipment and surfaces that have direct contact with sterile products and components sterilized by heat. Does it achieve a minimum of a six-log reduction of the BI spores?
108. What method is used to decontaminate the inner surface of the isolator barrier (e.g., vapor hydrogen peroxide, steam hydrogen peroxide, chlorine dioxide, etc.)? Determine decontamination parameters.
109. Did the surface decontamination validation study sufficiently address the ability of the sterilant to disperse throughout the chamber and reach all surfaces? Did the decontamination process include the use of Chemical Indicators (CI) to determine the presence or absence of the VHP on the work surfaces and/or the worst case locations to decontaminate? The CI can assist in the evaluation process by providing useful qualitative data. Were replicate BIs placed throughout the isolator, including the most difficult to reach locations (e.g., underneath any items remaining in isolator during sterilization). Are the most difficult to sterilize materials evaluated?
110. What is the isolator decontamination frequency and is it justified by validation data?
111. Is a decontamination cycle performed after a power failure or pressure reversal or other unanticipated breach of system integrity?
112. How often is the isolator decontamination cycle revalidated?
113. Does the written environmental monitoring program include routine tests for nonviable particles, as well as an appropriate number of microbial tests (e.g., active air and surface samples; gloves samples) during each campaign? Evaluate the tests performed and the testing frequencies.

#### **Testing Isolators (Sterility test).**

114. Have any false positives been identified in the laboratory isolator barrier (this should be an exceedingly rare occurrence)? Were the false positive investigated to determine and correct the cause.

#### **ENVIRONMENTAL MONITORING – Non-viable**

*Reference: FDA's 2004 Aseptic Processing Guidance, Section IV.*

115. Is the air supplied to critical areas (exposed product / filling areas) filtered through HEPA filters under positive pressure?

116. Is the air flow in critical areas unidirectional when delivered to the point of use? At what velocity? Is velocity determined at the critical work height and at the filter face? Air flow pattern evaluations (smoke studies) under dynamic conditions are performed to visualize and demonstrate unidirectional air flow within a designated area/room [e.g., Class 100 & 10,000 (ISO5 & ISO7)]. The smoke studies may also reveal air turbulences and air eddies that could be a vector assisting the dissemination of microbial and/or non-viable contamination within critical manufacturing areas.
117. How is the air filtered that is supplied to critical areas (where unsterilized product, in-process materials, and container/closures are prepared)?
118. What are the firm's air quality classifications for the following areas:
- Compounding
  - Equipment preparation
  - Any area where product or sterilized components are exposed
  - Areas where aseptic connections are made
  - Filling lines
  - Room surrounding filling lines
  - Capping (crimping) area
119. How often are HEPA filters integrity tested? What test method is used? What is done if leaks are found? If done by an outside firm, are results reviewed by on-site personnel including the quality unit?
120. How often are air flow velocities checked for each HEPA filter? What are the air velocity specifications? What is done if velocity readings are out of specification?
121. Does the firm have a written monitoring program for classified areas that includes scientifically sound sampling schedules; descriptions of sampling locations and frequency of sampling? How were the locations selected?
122. What type of instrument is used to check non-viable particle counts in the classified areas? Is the air sampled continuously? If continuous, is there an alarm when counts exceed pre-set limits or detects cleanroom doors open for an extended time? What is done in response to the alarms? Is there an alarm log? Are permanently installed sensors used or portable units that are taken into and out of the critical areas? What is done if counts meet or exceed alert and action limits?
123. What are the pressure differential requirements in the sterile core area? Does this assure an air cascade from most clean area to least clean air (by air classification)?
124. How are pressure differentials monitored? Is a continuous monitoring system used? If yes, does it include alarms so operators are aware of excursions? Are alarm conditions documented (alarm log)? What is done in response to an alarm? How long must a condition exist before an alarm sounded?

125. How are temperature and humidity monitored? What is the acceptable range? What is done if the reading is outside of the range?
126. How are environmental excursions (readings that meet or exceed alert and action levels) handled? Are the excursions investigated to determine impact on product, root cause and needed corrective actions?

### **ENVIRONMENTAL AND PERSONNEL MONITORING – Microbiology**

*Reference: FDA's 2004 Aseptic Processing Guidance, Sections V and X.A*

#### **Air.**

127. Does the firm have an effective Environmental Monitoring (EM) Program in place? What is the purpose and scope of the EM Program? Are EM sampling locations strategic, based on product contamination risk of the process and operation? Are the microbial alert and action levels based on the historical EM data derived from the manufacturing operations, support utilities and personnel practices performed at the manufacturing site? What is the frequency of microbiological sampling of air using "active" samplers (systems that sample a known volume of air) in various locations, such as:
  - Areas where product or sterile components are exposed to the environment
  - Filling areas
  - Loading areas for lyophilizers
  - Surrounding areas
128. What are the established microbial alert and action levels or limits for quantitative air samples? What is the length of the sampling period? Is sampling done during production or at rest?
129. What type of active air sampling equipment is used (centrifugal, impaction, membrane)? Is the sampling equipment calibrated? What is the efficiency of the active air sampler?
130. Does the firm have data on the ability of these samplers to recover organisms without deleterious effect on survivability such as through impact or desiccation of the media?
131. What is the actual volume of air sampled per location?
132. Are settling plates used? What is the length of exposure period? Sampling frequency? Locations (including proximity to critical operations)? Microbial limits?

#### **Surfaces.**

133. Are there written procedures that describe the monitoring of surfaces in the clean rooms? Does it describe locations, frequency and sampling techniques?
134. What surfaces are sampled in the critical (Class 100 / ISO 5) areas? Are critical surfaces included (those that touch the sterile product or sterile components)?

135. When are surface samples taken? Are critical surfaces only sampled at the end of the operation?
136. What is the frequency of sampling surfaces?
137. What types of samples are collected at each location (RODAC plate, swab samples)?
138. What are the alert and action levels / limits for the microbial sampling of critical surfaces, surfaces in Class 100 areas and surfaces in other classified areas? How were the levels / limits established? What is done when the samples meet or exceed alert and action levels?

**Personnel.**

139. Are there specific programs for training personnel who work in classified and aseptic processing areas? Does the program include microbiological testing or qualifying employees before they are allowed to work in these areas? Does the program include prequalification requirements?
140. How often is monitoring performed on filling room personnel? Is it done at least upon existing the cleanroom (e.g., per shift)? How often are gloves (hands) sampled? How often are gowns sampled? Is any sampling done after interventions are performed?
141. Who performs the sampling of personnel? Is it self-sampling? Is the sampling performed by another production employee, a microbiologist, technician or other quality control employee?
142. What are the firm's alert and action levels / limits for personnel monitoring? How were the levels / limits established? What is done if the sample results reach or exceed the alert and action limits?
143. Do employees spray their hands with sanitizer or disinfectant before the sample is taken?

**General.**

144. What are the microbiological growth media used for environmental and personnel monitoring samples?
145. Are the media used in the viable monitoring program shown to be capable of detecting molds and yeasts as well as bacteria by means of growth promotion tests?
146. Is anaerobic monitoring ever performed? When?
147. Are inactivators used for antibiotics or other bactericidal / bacteriostatic substances? Has the firm shown that these are effective? Are records available?
148. When are recovered microorganisms identified? To what level (genus, species)?
149. What are the incubation times and temperatures?
150. How are environmental and personnel monitoring data trended? How often are trend reports prepared? How often are they reviewed? Who reviews the trend reports? What type of action is taken based on review of trend reports?

151. Are environmental and personnel monitoring samples that exceed action levels investigated to determine product impact, cause and needed corrective actions? What is done when an alert level is exceeded?

Review and assess the EM trending data, which will provide a good indication if the viable and non-viable particles are maintained within the established levels or drifting out of control. What are the causes of the aberrant events? Were corrective actions and preventive measures taken to preclude the reoccurrence of the viable and non-viable particle anomalies?

### **BIOLOGICAL INDICATORS (BIs)**

In sterile drug manufacturing, BIs are typically used to validate the cycles used for terminal sterilization, sterilization of equipment and components. BIs are also used to validate SIP systems used to sterilize lyophilizers, processing tanks, sterilizing filters, and product lines and systems used to decontaminate surfaces in isolators.

152. What type of indicator is used (e.g., inoculated carrier, inoculated product, inoculated simulated product, etc.)? Are BIs inoculated into the components (i.e., stoppers) used whenever possible? What are their corresponding D values? Is the sterilization cycle adequate corresponding to the D value of the BI?
153. If the source of the indicator is commercial, what is the brand name and manufacturer? What labeling is received with the BI? If the BI is prepared in-house, determine the supplier of the organism, how the BI is propagated and stored, and the method of preparation?
154. What organism is used (Genus, species)? Is it the appropriate microorganism used for sterilization?
155. What is the challenge level of the biological indicator prior to exposure to sterilant?
156. Does the firm verify viable spore count on each lot of BIs before use in validation?
157. Does the firm or the BI labeling claim to meet USP performance criteria for steam or ETO biological indicators?
158. Does the firm perform USP testing on each lot of BIs received?
159. What is the approximate D-value of the biological indicator? Is this verified prior to validation?
160. How many BIs are used per sterilizer load?
161. What procedure is used to assay the indicators after exposure? What growth media is used? What are the optimal and actual incubation time and temperature for the BI (compare to COA received with the BI)?
162. How are the BIs prepared for sterilization?

163. Are biological indicators located in the most difficult to sterilize product sites (explain)? How are these locations determined?
164. Is there a diagram of the distribution of biological indicators in the loading pattern(s) used?
165. What is the elapsed time (hrs.) between removing indicators from the sterilizer and testing? Are there time limits established for this period? What happens if they are exceeded?
166. What is done if positive BIs are found after sterilization?
167. Describe biological indicator storage conditions:
- A. Type of room, cabinet, etc. (if stored in freezer or refrigerator, state if frost-free)
  - B. Temperature
  - C. Relative humidity (if known)
  - D. Compare to literature received with BI or written procedures
168. Does the firm use chemical process monitor(s) to indicate cycle exposure or to measure one or more cycle parameters?