

Guidance for Industry

Manufacturing Biological Drug Substances, Intermediates, or Products Using Spore-Forming Microorganisms

DRAFT GUIDANCE

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Guidance for Industry

**Manufacturing Biological Drug Substances, Intermediates, or
Products Using Spore-Forming Microorganisms**

This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic.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

I. INTRODUCTION

The former regulations at 21 CFR 600.11(e)(3) (§ 600.11(e)(3)) required that all work with spore-bearing microorganisms (spore-formers) be conducted in an entirely separate facility, or in a completely walled-off portion of a multiproduct facility. This isolated facility or building had to be dedicated exclusively for the manufacturing or storage of spore-formers. Previously, areas in a multiproduct facility used for manufacturing with spore-formers were required to be constructed to prevent cross-contamination of other areas, and were required to include entrances that were separate and independent from the remainder of the facility. All equipment used for manufacturing spore-formers was to be permanently identified and reserved exclusively for use with those microorganisms. Any materials destined for further manufacture were to be removed from this area only under conditions that prevented the introduction of spores into other manufacturing areas.

We, the Food and Drug Administration (FDA), modified the regulatory requirements for the manufacturing of biological products with spore-formers to allow greater manufacturing flexibility. Under the revised regulation¹ we no longer require the use of permanently dedicated facilities and equipment for spore-formers, if certain controls and precautions are applied. We recognize that advances in facility, system, equipment design, testing, and sterilization technologies have increased the ability of manufacturers to control and analyze the manufacture of biological products. As industry has gained experience with these new technologies, we found that manufacturers could evaluate aspects of a biological product’s safety and purity with testing. The use of appropriate

¹ In the *Federal Register* of December 30, 2003, FDA published for public comment the Direct Final Rule entitled, “Revision of the Requirements for Spore-Forming Microorganisms” (68 FR 75116), and the accompanying Proposed Rule entitled, “Revision of the Requirements for Spore-Forming Microorganisms; Companion to Direct Final Rule” (68 FR 75179). In the *Federal Register* of May 14, 2004, FDA published the “Revision of the Requirements For Spore-Forming Microorganisms; Confirmation of Effective Date” (69 FR 26768) confirming the effective date of June 1, 2004, for the direct final rule.

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controls, validated procedures and processes, and enhanced testing capability provide the manufacturer with a degree of confidence that their product achieves the expected levels of safety and purity. Areas of special concern, such as containment, contamination with pathogenic and/or toxic agents, sterilization, and disinfection can be addressed using currently available procedures and processes.

We recognize that spore-formers are currently used in manufacturing processes and there will likely be a need to use them in the immediate future. However, for the production of future products, manufacturers are encouraged to identify alternatives to the use of spore-forming microorganisms whenever possible. Such alternatives could include the use of sporulation deficient strains, or recombinant proteins expressed in nonspore-forming microorganisms. We anticipate that certain second-generation vaccines, including those against anthrax, botulism, and tetanus will likely contain recombinant proteins. This guidance document provides recommendations to industry to correspond with changes made to § 600.11(e)(3).

The revised regulation uses the term “spore-forming” microorganisms to describe organisms that are capable of spore production. The term “spore-bearing” microorganism, which was used in the earlier regulation, is not used because the term spore-forming microorganism is the more commonly accepted description of this class of microbes. For the purposes of this guidance, the term spore-forming microorganism (or “spore-former”) includes both the spore and vegetative forms of the organism.

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

II. SCOPE

The purpose of this document is to provide to you, manufacturers of biological drug substances, intermediates, or products using spore-forming microorganisms, guidance in response to changes made to § 600.11(e)(3). The revised regulation describes the requirements for manufacturing using spore-forming microorganisms and allows manufacturers greater flexibility than under the prior regulation.

This guidance applies to biological manufacturing processes utilizing spore-forming microorganisms. Once the biological drug substances, intermediates, or products have been separated from the viable spore-forming microorganism the concern of cross-contamination diminishes. We recommend that you establish a distinct crossover point in the separation process.

This guidance does not apply to allergenic and fungi source material, or therapeutics.

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This guidance does not apply to spore-forming microorganisms used for testing of biological products, such as testing the growth-promoting qualities of medium or the use of biological indicators in validation. This guidance does not apply to the requirements set forth in §§ 600.11(e)(2) and 610.12 (21 CFR 610.12).

When the spore-former used in the manufacturing process is a pathogen or potentially pathogenic, the stricter requirement between § 600.11(e)(5) and revised § 600.11(e)(3) must be applied.

III. BACKGROUND

Spore-formers are used in the production of certain biological products. Biological drug substances or intermediates derived from these organisms may be used as source material for further manufacture into final products such as vaccines. Bacteria produce spores as a means to survive adverse environmental conditions. In general, spores show enhanced resistance over bacteria to high temperatures, freezing, dryness, antibacterial agents, radiation, and toxic chemicals. Under favorable conditions, spores can germinate into actively growing vegetative bacterial cells. Some of these spore-formers are human pathogens and are associated with high morbidity and mortality. Due to their unique survival properties, spore-formers pose great challenges to manufacturers. In order to ensure the safety of a biological product manufactured in a facility in which spore-formers are present, these microorganisms must be kept under stringent control in order to avoid the release of spores into the manufacturing area where they have the potential to cross-contaminate other products. [§ 600.11(e)(3)(i)].

Manufacturing with spore-formers requires varying levels of control depending on the characteristics (e.g., virulence toward humans) of the microorganism that is utilized in a manufacturing process. You are encouraged to institute the appropriate precautions in the manufacturing facility, associated equipment, and manufacturing procedures to avoid contamination. The recommendations and precautions described in this guidance are intended for manufacturing with the type of spore-formers that are currently used by the regulated industry and included in the scope of this guidance. Any atypical or novel spore-formers may require specific controls that are unique for that particular organism.

Processing and propagation of spore-formers must be conducted in areas and using systems not used for any other purpose at the same time. [§ 600.11(e)(3)]. These areas must be cleaned using validated procedures. [§ 211.67 (21 CFR 211.67)]. Prior to initiation of processing and propagation, it is important to establish containment and demonstrate control of spore-forming microorganisms in order to prevent the spread of the spore-former. Containment is established by facility design and/or the use of procedures and equipment that prevent the release of spores into adjacent areas.

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[§ 600.11(e)(3)(i)]. You are required to verify containment through spore-former specific testing and monitoring to provide a level of assurance that the spore-former does not cross-contaminate other products or areas in the manufacturing facility.

[§§ 600.11(e)(3)(i); 211.42(b) and (c); 211.100; 211.113; 211.165(d)].

In order to prevent cross-contamination of other products, products derived from spore-formers must not be removed from designated areas unless they can be removed in such a manner as to prevent cross-contamination. [§ 600.11(e)(3)]. Prior to use for other products, these areas, including equipment, must be properly cleaned and decontaminated using validated processes to ensure that cross-contamination of the subsequently manufactured products does not occur. You must also use validated processes to address areas of special concern, such as containment, contamination with pathogenic and/or toxic agents, sterilization, and decontamination. [§§ 600.11(e)(3)(ii); 211.42(c); 211.67; 211.100; 211.113].

IV. MANUFACTURING WITH SPORE-FORMERS IN A DEDICATED FACILITY

This section applies if you choose to use a separate dedicated building or facility configuration for manufacturing with spore-formers. Although you are no longer required to use that type of configuration, if you do so, you must follow the applicable requirements in § 600.11(e)(3)(i) to avoid having to satisfy the process containment requirements in subsection (e)(3)(ii). This section reiterates the requirements in subsection (e)(3)(i) applicable to dedicated buildings/facilities, and provides additional recommendations for using that configuration.

A. Facilities and Equipment

The use of a separate dedicated facility or a dedicated building annex for manufacturing processes involving spore-formers is the simplest means to prevent cross-contamination. The separate building or facility configuration is not intended to accommodate the manufacturing of multiple products using spore-formers. If multiple products are manufactured in the same area or within the same building using spore-formers, then additional criteria will apply. See § 600.11(e)(3)(ii) and Section V. below.

1. Containment

a. Building Construction and Configuration

If you choose to use a separate building or facility configuration for manufacturing processes involving spore-formers, your dedicated building or facility must be completely walled off and constructed as to prevent contamination into other buildings or portions of the same building.

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[§ 600.11(e)(3)(i)]. Being completely walled off means having walls that extend to the roof, having no shared mezzanine or above ceiling spaces with non-dedicated areas, and having an independent entrance.

We recommend that all surfaces be solid, hard, non-porous, and cleanable, including ceilings and walls. To the extent you are using aseptic processing, § 211.42(c)(10)(i) requires you to have floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable. Please refer to FDA's guidance for industry entitled "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice," dated September 2004 (October 4, 2004, 69 FR 59258) (<http://www.fda.gov/cder/guidance/5882fml.htm>), for the agency's current thinking on aseptic processing.

b. Air Handling Units (AHUs)

AHUs cannot be shared with other buildings or portions of the building. [§§ 600.11(a); 600.11(e)(3)(i)]. Dedicated re-circulating AHUs are acceptable within the dedicated facility. We recommend that exhaust not be located near other AHU intakes. We also recommend that you consider using high-efficiency particulate air (HEPA) filtration of exhaust, and that you maintain the building at negative pressure with respect to the outside environment and/or adjacent areas.

c. Equipment Dedication

If you choose a separate dedicated building/facility configuration, major equipment must be identified as used for manufacturing with the particular spore-former. [§ 211.105(b)]. We recommend that you dedicate all equipment in the building/facility.

2. Procedural Control

a. Personnel Gowning and Flows

We recommend that personnel who work in manufacturing using spore-formers shower and complete a "clean" clothing change prior to entering other areas of the facility or interacting with personnel not directly involved in the manufacturing of spore-formers.

b. Material Transfer

We recommend that any material transferred out of a spore-former manufacturing facility that may cross-contaminate other products, product containers, intermediates, or materials used in the manufacturing of other products be decontaminated via a decontamination chamber prior to exiting

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the facility. If a decontamination chamber is not feasible, then a series of airlocks utilizing surface decontamination with an appropriate agent may be acceptable.

When utilizing a decontamination chamber system such as an autoclave, sterilize-in-place (SIP) cycle, or gas chamber, the decontamination cycle must be validated to inactivate the spore-former. [§§ 211.100; 211.113]. We recommend that you incorporate a worst-case approach. You may not use the same chamber for both the decontamination of the spore-former and the sterilization of other production items. [§ 600.11(e)(i)].

When it is necessary to employ an airlock system for decontamination of material that is transferred out of a facility, the decontamination process, using a liquid or gaseous agent, must be validated to inactivate the spore-formers, including decontamination agent efficacy studies. [§§ 211.100; 211.113]. We recommend that you incorporate a worst-case approach. We also recommend that you consider parameters that include the composition of the material, exposure time, concentration, pH, temperature and any other relevant factors. If the airlock system involves only local decontamination of the equipment or item, such as wipe downs, then we recommend that the decontamination process be conducted and validated in series (multiple airlocks) to ensure that no trailing contamination is encountered. We recommend that inside personnel pass the outgoing material and/or equipment into an interior material airlock (i.e., Material Airlock (Primary Decontamination) as shown in Appendix A), where they decontaminate the items according to approved validated procedures. After initial decontamination, the inside personnel transfer the outgoing items into an exterior material airlock (i.e., Material Airlock (Secondary Decontamination) as shown in Appendix A). The outside personnel then provide a second decontamination step (also validated) on the outgoing items, and then transfer the material and/or equipment into an exit corridor or room. We recommend that temporal separation between personnel be maintained and that personnel not use material airlocks for exiting (See Appendix A).

c. Equipment Cleaning

No special equipment cleaning, beyond what § 211.67 requires, is needed when manufacturing with spore-formers, provided that the equipment is maintained within the dedicated processing area.

B. Waste Disposal

Process waste can be treated in a similar fashion as the material transferred out of the facility or processed through a validated bio-waste system. When waste is transferred out of the facility, we recommend that it be transferred out in biohazard bags via

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multiple airlocks in a manner similar to the material transfer process described in Section IV.A.2.b. We recommend that waste be bagged in the processing room and transferred to the interior material airlock where the outside of the bag is decontaminated by the inside personnel. After the initial decontamination, inside personnel put the bagged waste into another biohazard bag and transfer it into the exterior material airlock. Outside personnel decontaminate the outside of the second biohazard bag and remove the double-bagged waste from the exterior material airlock (See Appendix A).

We recommend that all waste be disposed of in a manner that is in compliance with federal, state, and local environmental laws.

V. MANUFACTURING WITH SPORE-FORMERS IN A MULTIPRODUCT MANUFACTURING AREA USING A NON-DEDICATED FACILITY: PROCESS CONTAINMENT

Process containment is designed to isolate equipment or an area that involves manufacturing using spore-forming microorganisms mechanically (Containment) and procedurally (Process Control). This isolated manufacturing area, including product, equipment, or material storage in that area, must not be used for any other purpose during the processing period. [§ 600.11(e)(3)(ii)]. The isolated manufacturing area shall contain adequate space and equipment for all processing steps. [§ 211.42(b)]. If you intend to use an area for manufacturing spore-formers and other products on a campaign basis, then you must develop and execute extensive validation studies to demonstrate containment and decontamination before initiating processing of other products in that manufacturing area. [§§ 600.11(e)(3)(ii); 211.42(c)(5); 211.100]. These validation studies must, at a minimum, support your procedures for containment, monitoring, cleaning, decontamination, and movement of materials in and out of that area. [§§ 211.42(b) and (c); 211.67; 211.100; 211.113; 600.11(e)(3)]. You must follow those validated campaign changeover procedures whenever an area that was previously used for a spore-forming microorganism will subsequently be used for manufacturing other products.

A. Facilities and Equipment

1. Containment

a. Building Construction and Configuration

We recommend that the isolated areas have double serial entry, exit, and material airlocks to minimize the potential for cross-contamination via personnel, materials, and air turbulence. As shown in Appendix A, the interior airlocks would serve as an air sink for the primary decontamination step. The three air sinks shown in Appendix A include the final gowning step

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(Gown-in (Final)), the gross de-gowning step (Gown-out (Initial)), and the interior material airlock (Material Airlock (Primary Decontamination)). The exterior airlocks would serve as an air dome for the preliminary gowning step. The air domes shown in Appendix A include primary decontamination (Gown-in (Preliminary)), the final de-gowning step (Gown-out (Final)), and the secondary decontamination step (Material Airlock (Secondary Decontamination)).

We recommend that all surfaces be solid, hard, non-porous, and cleanable, including ceilings and walls. To the extent you are using aseptic processing, § 211.42(c)(10)(i) requires you to have floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable. We recommend that the final ceiling and wall finishes minimize air leaks.

All tables, shelving, and storage apparatus must be designed to facilitate decontamination. [§ 600.11(e)(3)(ii)].

b. Air Handling Units (AHUs)

We recommend that AHUs using 100% single-pass air be used within the isolated area, and that the isolated area be maintained at a negative air pressure to all surrounding areas, including ceilings and mechanical spaces. We recommend that exhaust not be located near other AHU intakes, and that HEPA filtration of exhaust be considered.

c. Equipment Dedication

Wherever possible, we recommend that major processing equipment be dedicated for a specific product use. Such equipment must be identified to show the specific equipment used in the manufacture of each batch of product. [§ 211.105]. If equipment is dedicated for a specific manufacturing process using a spore-former, it must be decontaminated prior to the introduction of a new production process [§ 600.11(e)(3)(ii)], and we recommend removing it from the area, where feasible. We recommend that dedicated equipment be segregated from other equipment while in storage.

We recommend that small ancillary equipment and administrative items such as pens, logbooks, pipettes, miscellaneous glassware, and standard operating procedures (SOPs) be dedicated or made disposable. Dedicated and disposable items must be decontaminated and/or removed from the processing area during the area changeover procedure. [§ 600.11(e)(3)(ii)].

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When equipment dedication and removal is not feasible, such as with large fixed mounted bioreactors, a validated decontamination and cleaning procedure must be in place. [§§ 600.11(e)(3)(ii); 211.67; 211.100; 211.113]. See also Section V.A.2.c. below.

2. Procedural Control

a. Personnel Gowning and Flows

We recommend that personnel entry and exit flows be unidirectional. We also recommend that personnel gown with multiple layers so that personnel gowning and de-gowning occurs in multiple stages (See Appendix A). Gowning procedures are designed to prevent or reduce the potential for personnel to carry the spore-former out of the area via their hair, skin, shoes, jewelry, or clothing. Disposable gowning must be decontaminated using a validated process or adequately bagged and sealed prior to leaving the isolated area. [§§ 600.11(e)(3)(ii); 211.100]. Personnel who work with spore-formers are recommended to shower and complete a “clean” clothing change prior to entering other areas of the facility or interacting with personnel not directly involved in the manufacturing of spore-formers.

b. Material Transfer

The requirements for material transfer in a multiproduct manufacturing facility are the same as those for a dedicated facility (See Section IV.A.2.b.).

c. Equipment Cleaning

When the use of dedicated or disposable equipment is not feasible, such as with large or fixed bioreactors, validated decontamination and cleaning procedures must be in place. Validation of these procedures must include the following:

- efficacy of the decontamination;
- analysis of potential residue for the specific spore-former; and
- evaluation of product contact surface areas, and the interior and exterior areas on equipment to include controls, valves, seals, probes, motors, wiring harnesses, and miscellaneous external surfaces.

[§§ 600.11(e)(3)(ii); 211.67(b); 211.100].

We recommend the dismantling and inspection of such equipment between different products. The harshness of cleaning agents (e.g., NaOH) can lead to pitting of equipment and may protect spore-formers from the decontaminant.

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B. Waste Disposal

The recommendations for waste disposal in a multiproduct manufacturing facility are the same as those for a dedicated facility (See Section IV.B.).

C. Campaign Changeovers

Campaign changeovers involve the cleaning and decontamination of a specific area that has been exposed to a spore-former in preparation for the introduction of another product or process into that same area. The decontamination and cleaning would include all equipment and items that may have been exposed to the spore-forming microorganism. This includes Biological Safety Cabinets and re-circulating AHUs. In addition, consideration may be given to decontamination of the entire manufacturing area with a gaseous sterilant such as chlorine dioxide or hydrogen peroxide.

Prior to introducing a new product into a facility previously used to manufacture spore-formers, you must develop and execute extensive validation studies that focus on issues related to containment, decontamination, monitoring, cleaning, and movement of equipment and materials in and out of that area. [§§ 600.11(e)(3)(ii); 211.42(b) and (c); 211.67; 211.100; 211.113]. Campaign changeovers as outlined in this document occur when an area that was previously used for spore-former manufacturing will subsequently be used for manufacturing with any other FDA-regulated product.

We recommend that the following required procedures be completed in the order indicated below for cleaning and decontamination of an area that is to be used on a campaign changeover:

- 1) all waste in the area is removed or sent to the bio-waste system, as required by § 600.11(e)(3)(ii);
- 2) stay-in place equipment is decontaminated, as required by § 600.11(e)(3)(ii);
- 3) removable dedicated equipment and ancillary items are decontaminated and removed or sent to waste for disposal from the area according to approved and validated material transfer procedures, as required by § 600.11(e)(3)(ii) and as outlined with additional specific recommendations in Section IV.A.2.b.;
- 4) room and room fixtures (e.g., shelves, incubators, storage units) are decontaminated and cleaned according to an approved validated process, as required by §§ 600.11(e)(3)(ii), 211.67(a), 211.100, and 211.113;
- 5) stay-in-place processing equipment is dismantled, cleaned, and sterilized (if applicable), as required by §§ 600.11(e)(3)(ii) and 211.67;
- 6) monitoring specific for the spore-formers used in manufacturing is performed, as required by § 600.11(e)(3)(ii) (See Section V.D. for additional recommendations); and

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- 7) a quality control unit review of the campaign changeover data (including monitoring results) and a quality control unit area inspection is executed prior to releasing the area for the next product, as required by § 211.22(c).

D. Sampling and Testing

On-going sampling and testing for spore-formers in the facility, equipment, and subsequent products manufactured is important to ensure containment and cleaning procedures are continuously effective. Environmental monitoring is a program designed to test the manufacturing environment, including equipment, manufacturing areas, and personnel, to detect contaminants. An adequate environmental monitoring program identifies contaminants, allowing for implementation of corrections before product contamination occurs. Product monitoring is testing performed on FDA-regulated products as a means to ensure freedom of contaminants.

Environmental monitoring that is specific for the spore-former must be conducted in the areas adjacent to the isolated processing area during manufacturing steps involving the organism. In addition, environmental monitoring specific for the spore-former must be conducted in the isolated processing area at the end of the campaign changeover procedure to qualify the area for release. [§§ 600.11(e)(3)(ii); 211.100]. Finally, we recommend that you consider testing subsequent products manufactured for the presence of the spore-former.

1. Testing and Sampling Qualification

For both environmental and product monitoring to uniquely identify a spore-former used in a manufacturing process, as § 600.11(e)(3)(ii) requires, that monitoring must be qualified for specificity, sample recovery, and detection limits, at a minimum. A quantitative or qualitative test is acceptable provided the test can be appropriately qualified. [§§ 211.160(b); 211.165].

a. Specificity

Testing must be able to detect the specific spore-former and identify it in the presence of other microorganisms. [§§ 600.11(e)(3)(ii); 211.160(b); 211.165(a), (b), (d), and (e)].

b. Sample Recovery

Sampling qualifications must demonstrate the percent recovery of the specific spore-former. [§§ 600.11(e)(3)(ii); 211.160(b); 211.165(d) and (e)].

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c. Detection Limit

Limits of detection using the specific spore-former must be established. [§§ 600.11(e)(3)(ii); 211.160(b); 211.165(c) through (e)].

2. Environmental Monitoring

a. Frequency

Specific testing and sampling for spore-formers must be conducted both during manufacturing operations and at the conclusion of the campaign changeover procedures. [§ 600.11(e)(3)(ii)]. During operations, we suggest that the sampling and testing be conducted in the adjacent areas at the beginning, middle, and end of each manufacturing shift.

b. Sample Locations

We recommend that adjacent areas, associated with the isolated processing area, be sampled near or at the points of possible egression, such as doorways, windows, and/or other openings.

We recommend that the number of samples for testing at the end of the campaign changeover be developed by a matrix approach and take into account the size and complexity of the equipment, room, and room fixtures. We suggest that the exact sampling sites be determined based on equipment and items that are the most difficult to clean and decontaminate and the likelihood of product impact. For example, controls over a formulation tank should be tested, but the floor in an isolated corner may not need to be included.

3. Monitoring

Environmental monitoring levels and product monitoring limits must be set to ensure manufacturing areas, adjacent areas, personnel, and other products are not contaminated with spore-formers. [§§ 600.11(e)(3)(ii); 211.42; 211.113].

Environmental monitoring levels are set based upon the need to maintain adequate control throughout the manufacturing facility. Alert and action levels are used to ensure the manufacturing operations are in a state of control. Specific alert levels are set for monitoring that is not necessarily specific to spore-formers, but for all possible microorganisms that may be present. Alert levels will vary depending on the characteristics of the microorganism. Considerations such as specific microorganism's virulence, resistance, and growth conditions are used to set environmental monitoring levels. We

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recommend that alert levels be calculated using your monitoring sampling and testing recovery data and the qualified limit of detection of the test method employed. When possible, we recommend that alert levels be established using historical data.

Monitoring of products manufactured subsequent to spore-forming microorganisms or in adjacent manufacturing areas also provides for assurance the facility and processes are in a state of control. This monitoring is specific to the spore-former.

All test results that do not conform to the alert or action levels or product monitoring limits set must involve an immediate response and subsequent investigation. [§ 211.100(b)]. You must have procedures in place detailing the response and subsequent investigation. [§§ 211.22(a) and (d)]. We recommend that the initial response attempt to keep the spore-former from spreading to other parts of the facility, building, or site. Subsequent responses should involve cleaning and decontaminating the infected area or equipment. You must investigate the cause of the excursion, evaluate product impact, and prescribe corrective action and follow-up sampling. [§§ 211.22; 211.192].

VI. SPILL CONTAINMENT

Approved procedures must be in place to address emergency responses for all spills involving spore-forming microorganisms regardless of location, including packaging lines and finished product storage. These responses must include validated procedures for containing the spill, and cleaning and decontaminating the area and equipment affected by the spill. [§§ 600.11(e)(3); 211.42; 211.67; 211.100; 211.113].

VII. MAINTENANCE AND DECOMMISSIONING

A. Maintenance

Maintenance activities must be performed in a manner as not to spread the spore-former to other manufacturing areas or break the integrity of the process containment. If it is necessary to break the integrity of the process containment to perform maintenance activities, then you must execute the decontamination procedure prior to the maintenance activities and after all manufacturing activity has ceased. [§§ 600.11(e)(3); 211.67(a); 211.100; 211.113].

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B. Decommissioning

Decommissioning of a dedicated spore-former manufacturing area or building must involve a comprehensive decontamination plan with extensive spore-former specific testing to ensure the adequate removal and/or cleaning of the area and building prior to the introduction of another product (See Section V.D.). [§§ 600.11(e)(3)(ii); 211.67].

VIII. DEFINITIONS

- a. Air handling unit (AHU) – A component of the HVAC system that includes the fans, filters, coils, and other materials used to generate conditioned air.
- b. Action level – An established microbial level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.
- c. Alert level – An established microbial level giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are always lower than action levels.
- d. Campaign changeovers – The process of cleaning and decontaminating a specific area, equipment, system, waste, and/or ancillary items exposed to a spore-forming microorganism in preparation for the introduction of another product or process into that same area.
- e. Containment – Physical/mechanical barriers and/or systems designed to control spore-formers to prevent contamination.
- f. Cross-contamination – Contamination of a material or product with another material or product.
- g. Crossover point – The processing point where viable organisms are not part of the process or process solutions.
- h. Decontamination – The inactivation of the living organism and any associated toxic material through chemical and/or physical means.
- i. Biological drug substance – Any substance or mixture of substances intended to be used in the manufacture of a drug (biological) product and that, when used in the production of a drug product, becomes an active ingredient of the drug product. Such substances are applicable to the prevention, treatment, or cure of a disease or condition of human beings.

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- j. Intermediates – A material produced during steps of the processing that must undergo further molecular change or purification before it becomes a drug substance. Intermediates may or may not be isolated.
- k. Manufacturing site – Defined as the entire complex of buildings, connected or separate, and belonging to one entity engaged in the manufacturing of any one product or multiple products.
- l. Manufacturing facility – Defined as the physical structure associated with the manufacturing of any one product or multiple products.
- m. Manufacturing area – Defined as a specified location within a facility associated with the manufacturing of any one product or multiple products.
- n. Multiproduct – More than one approved product, licensed product, investigational new drug product or separate process.
- o. Procedural control – Manufacturing procedures executed in such a manner as to prevent or minimize spore-former contamination.
- p. Spore-forming microorganism – Any bacteria species that is capable of spore production. Species of spore-forming microorganisms that have been rendered incapable of spore production through mutation are no longer considered spore-formers.
- q. Qualification – Action of proving and documenting that equipment, ancillary systems, or areas are properly designed, installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.
- r. Validation – A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

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APPENDIX A: SPORE-FORMING MANUFACTURING DIAGRAM

→ = Airflow direction

