



May 25, 2005

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: [Docket No. 2003N-0528] – **Draft Guidance for Industry: Manufacturing Biological Drug Substances, Intermediates, or Products Using Spore-Forming Microorganisms; Availability**

Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of developing Merck product candidates derived from microorganisms, Merck scientists address topics covered in this proposed Guidance. We have extensive experience in the development, licensure and marketing of products manufactured using microorganisms and have utilized that experience to author the comments below.

Merck commends the Food and Drug Administration (FDA) for updating regulations and providing guidance on the use of spore-forming microorganisms in the manufacture of certain biological products. Our specific comments on the draft guidance follow.

**Section II, Document Scope.** Throughout the document, the term "spore-forming" microorganism is used. We suggest this term be clarified in Section II to make it clear that the guidance only applies to endospore-forming microorganisms. Additionally, we recommend adding wording to the scope that makes an exception for organisms that produce spores of hyphal origin (conidia).

For clarity, we recommend wording changes from "*The purpose of this document is to provide you, manufacturers of biological drug substances, intermediates, or products*

*using spore-forming microorganisms, guidance in response to changes made to §600.11(e)(3).” to “The purpose of this document is to provide you, manufacturers of biologicals (biological drug substances, intermediates, and/or products) made using endospore-forming microorganisms, guidance in response to changes made to §600.11(e)(3).”*

*“This guidance applies to biological manufacturing processes utilizing spore-forming microorganisms”*. Even though it is relatively clear that this guidance applies to the manufacture of biologicals using spore-formers in a dedicated or a multi-product facility, there is some concern that the principles therein may be extrapolated to the manufacture of biologicals occurring in the vicinity of spore-forming processes. We recommend a clarification that the guidance does not apply to the manufacture of biologicals in the vicinity of spore-forming processes. It is recognized that appropriate GMP cross contamination prevention controls may be applicable. We suggest the wording be changed to “This guidance applies to biological manufacturing processes utilizing spore-forming microorganisms campaigned in the same equipment in multi-product facilities or in specifically dedicated facilities”. An additional comment on this point may be found below in our comments to Section V.

**Section III Background:** To avoid unnecessary emphasis, we recommend deleting the word “great” from the text as follows *“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)].”*

The introduction discusses the concept that lesser containment requirements may be appropriate if there is the ability to *“evaluate aspects of a biological product's safety and purity with testing”* and other controls and attributes that can be used to give a *“degree of confidence that their product achieves the expected levels of safety and purity”*. In the remainder of the document, however, there is no acknowledgement that there are some manufacturing schemes appropriate (with justification) for these lesser requirements. We suggest that the first sentence of the second paragraph in the Background section be broadened to state (new wording underlined): *“Manufacturing with spore-formers requires varying levels of control depending on the characteristics (e.g., virulence toward humans) of the microorganism and the level of confidence that the specific process will yield product of the expected levels of safety and purity.”* Likewise, acknowledgement that specific cases may, with justification, allow for lesser controls should be added throughout Sections III-VII of this document.

*“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 addition to specific testing and

monitoring, physical methods should also be allowed as a means for verifying containment.

**IV. Manufacturing with Spore-Formers in a Dedicated Facility** **A. Facilities and Equipment** **1. Containment** **a. Building Construction and Configuration** *“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.”* As written, this statement is too prescriptive in directing how to achieve total containment. The compliance requirements should be stated and firms should have flexibility to determine the best ways to achieve ‘total containment’ based on the firm’s operations. We suggest this statement be eliminated or clearly state this description is an example.

**IV.A.2. Procedural Control** **b. Material Transfer** *“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)]”*. Using the same chamber should be allowable with validated cycles which inactivate the spores and proper controls in place to ensure contamination does not occur in the surrounding areas outside the sterilizer. We suggest this statement be clarified to read *“You may not use the same chamber for both the decontamination of the spore-former and the sterilization of other production items unless adequate controls and validated cycles are in place [§ 600.11(e)(i)]”*

*“We recommend that temporal separation between personnel be maintained and that personnel not use material airlocks for exiting (See Appendix A).”* As written, the sentence is too prescriptive. Technically supported alternate approaches should be allowed.

**IV. B. Waste Disposal.** *“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).”* As written, this section is too prescriptive. We recommend a more generic discussion covering waste disposal that speaks to the necessary controls required without prescribing the methods to accomplish.

**V. Manufacturing with Spore-Formers in a Multiproduct Manufacturing Area Using A Non-Dedicated Facility.** This section provides specifics for manufacturing in a multiproduct facility on a campaign basis, but the guidance is not clear in excluding from its scope a non-dedicated multi-product facility: where firms may have processing occurring in adjacent vessels such as in a fermentation suite with no open operations or open sampling. As we noted above (comment Section II Document Scope) there is some concern that the principles in this guidance may be extrapolated to the manufacture of biologicals occurring in the vicinity of spore-forming processes. We recommend a

clarification that the guidance does not apply to the manufacture of biologicals under GMP conditions in the vicinity of spore-forming processes.

*“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)].”* There is no specific definition of an isolated area or when isolated areas are required. Moreover, it seems that the suggested design of the isolation areas exceeds what is needed to call the processing area a separate facility. Clarification is needed in this section.

**V.A.1.c. Process Containment Equipment Dedication.** We suggest changing the wording as follows: from *“Wherever possible, we recommend that major processing equipment be dedicated for a specific product use”* to *“Wherever possible, we recommend that major processing equipment located within the spore containment envelope be dedicated for a specific product use.”* For example, use of a continuous sterilizer upstream of multiple suites should be satisfactory if it is located outside the spore containment envelope.

*“Such equipment must be identified to show the specific equipment used in the manufacture of each batch of product.”* The requirements for equipment use should be stated more generally with a focus on compliance with containment needs. Manufacturers should determine the methods for aligning with the compliance requirements.

**V.C. Campaign Changeovers.** *“5. stay-in-place processing equipment is dismantled, cleaned, and sterilized (if applicable), as required by §§ 600.11(e)(3)(ii) and 211.67”.* It may not be necessary to dismantle all stay-in-place equipment to adequately clean and sterilize it.

**V.D. Sampling and Testing 2. Environmental Monitoring a. Frequency** *“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.”* This level of sampling may not be appropriate for all circumstances. We recommend that the compliance requirements be stated (as they are in the previous sentence in this section) and that manufacturers be allowed to design environmental monitoring programs to align with the compliance requirements relative to their specific facility, processing areas, etcetera.

### **Conclusion**

In summary, we support the development of this guidance document to facilitate the implementation of the spore-former final rule. The rule change and the guidance reflect the forward thinking of the Agency based on increased knowledge and advances in technologies. We have identified areas for further clarification and have commented on specific potential issues. To address the need for further clarification of these points, we recommend the guidance be revised as noted herein.

We appreciate the opportunity to share our comments with respect to the FDA Draft Guidance for Industry; Manufacturing Biological Drug Substances, Intermediates, or Products Using Spore-Forming Microorganisms. Please do not hesitate to contact me, should you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "B. Rogalski-Salter". The signature is written in a cursive style with a large initial "B" and a long horizontal stroke.

Taryn Rogalski-Salter, PhD  
Director  
Regulatory Policy