Making American Healthcare More Affordable

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Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Docket No. 03D-0382
Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing

Comments of the Generic Pharmaceutical Association

Dear Sir or Madam:

The Generic Pharmaceutical Association (GPhA) appreciates the opportunity to comment on the above referenced draft guidance on aseptic processing. GPhA represent 98% of generic drug manufacturers whose drugs are dispensed for over half of all prescriptions filled in the United States, but representing less than 10% of all drug expenditures. GPhA is the united voice of the generic drug industry and is committed to patient health and safety, and strongly supports any measures that will improve our health care system. GPhA would like to thank the Agency for this opportunity to provide feedback on the draft guidance in an effort to clarify manufacture of sterile products.

GPhA appreciates the FDA's comprehensive treatment of this complex and important cGMP issue. Generally, the generic industry supports the draft guidance, however, we provide the following specific comments:

1. Section VIII. Time Limitations

In lines 679-684, the issue of upstream endotoxin load is addressed. We believe that this is superfluous for the following reasons: The possible source of endotoxin in the bulk formulation is microbial contamination of the ingredient components. As endotoxin presence is only an issue for injectable formulations, and ingredient components used to formulate injectables are checked for endotoxin levels, the only manner that endotoxin load could increase in a bulk material is by proliferation of the formulated bulk bioburden. Therefore the bioburden testing that is routinely performed on prefiltered bulk solutions also serves as an indication of possible endotoxin load excursions. Extra testing for endotoxin load is not justified and reference to it should be deleted from these

lines.

2. IX. Validation of Aseptic Processing and Sterilization, A. Process Simulations, 2. Frequency and Number of Runs, lines 758-760

The phrase "All personnel who enter the aseptic processing area" is too broad. This could include personnel who are not involved in aseptic processing such as cleaning crew, personnel who perform HEPA testing during production down times, and all support crew who are not directly involved in the aseptic process. We recommend that the sentence should be reworded to clarify that only personnel directly involved in the aseptic processes leading to the manufacture of aseptic products, including technicians and maintenance personnel, should participate in media fills, at least once per year.

3. IX. Validation of Aseptic Processing and Sterilization, A. Process Simulations, 8. Incubation and Examination of Media-Filled Units, lines 877-878

The phrase "training and experience in microbiological techniques" implies that only microbiologists/personnel with microbiology background can perform the task. Experience in Microbiological techniques is not an essential qualification for personnel to enable them to inspect media fill units for contamination. We recommend deleting the phrase and replacing with "appropriate training and experience in detecting microbial contamination."

4. IX. Validation of Aseptic Processing and Sterilization, A. Process Simulations, 7. Media, lines 848-850

The intent is not clear in the sentence "For those instances in which the growth promotion testing fails, the origin of any contamination found during the simulation should nonetheless be investigated, and the media fill should be promptly repeated." Should the media fill be repeated if growth promotion fails or when there is contamination? In either case repeating the media fill is not warranted unless the media fill contamination is higher than the recommended criteria for assessing the state of aseptic line control (page 27 of the draft guidance). Failure of growth promotion could be due to very low inoculum levels or non-viable inoculum, which would be indicated by a concurrently run enumeration of inoculum. To repeat a media fill without reviewing the cause of the growth promotion failure is excessive. Similarly, to repeat a media fill if only one unit is contaminated in 5,000-10,000 units is excessive. As such, we recommend deleting this sentence and replacement with language to suggest investigation of growth promotion failure and appropriate corrective action.

5. IX. Validation of Aseptic Processing and Sterilization, A. Process Simulations, 9. Interpretation of Results, lines 937-939

Regarding the statement that when filling 5,000 to 10,000 units "1 contaminated unit should result in an investigation, including consideration of a repeat media fill" we agree that one contaminated unit out of a minimum of 5,000 units (0.02% contamination) should result in a thorough investigation, but to repeat a media fill is excessive. As such we recommend deleting the reference to repeating the media fill.

6. IX. Validation of Aseptic Processing and Sterilization, C. Sterilization of Equipment and Container Closures, 2. Equipment Controls and Instrument Calibration, lines 1117-1118

The requirement to confirm the D-value of a Biological Indicator before every validation run is not only excessive but also contradicts the USP recommendation for reconfirmation of D-value every 12 months. It is common industry practice to confirm the microbial count prior to a validation and as such we recommend deleting confirmation of D-value prior to every run or harmonize this issue with USP.

7. X. Laboratory Controls, A. Environmental Monitoring, 3. Sanitization Efficacy, lines 1225-1227

The draft guidance states "The effectiveness of sanitizing agents and procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces (e.g., via obtaining samples before and after sanitization.)" In an operating clean room maintained within aseptic environmental control, sampling "before sanitization" would typically yield none/low number of isolates. Hence the base line for comparing the "after sanitization" number would be so low that a significant log reduction in microbial count could not be demonstrated. As such, this method of evaluation would not work in clean rooms with good environmental control. We recommend the language be changed to suggest that other equivalent methods may be used.

8. X. Laboratory Controls, A. Environmental Monitoring, 4. Monitoring Methods, a. Surface Monitoring, lines 1248-1249

The draft guidance states that ceilings should be tested on a regular basis. This is not always possible, such as for rooms with ceilings having 100% HEPA filters. As such we recommend the language be changed to address situations where testing ceilings is not appropriate.

9. X. Laboratory Controls, B. Microbiological Media and Identification, line 1309.

The draft guidance states: "Incoming lots of environmental monitoring media should include positive and negative controls." If growth promotion is performed on the media

batch, there should be no requirement for positive control. We recommend that the guidance provide the option of growth promotion of incoming batches of media in place of a positive control.

10. Appendix 2: Blow-Fill-Seal Technology, A. Equipment Design and Air Quality, lines 1779-1781

We recommend deletion of the reference to "polymer sterilization" from the list of items requiring qualification and validation studies. The polymer is normally not subject to a separate sterilization process per se. The appropriate process to be qualified and validated would be the polymer extrusion process.

11. Appendix 2: Blow-Fill-Seal Technology, C. Batch Monitoring and Control, lines 1796-1797

The statement "Microbial air quality is particularly important" should be deleted. Microbial air quality is important to any aseptic process, but the presence of this sentence implies some special importance in Blow-Fill-Seal. This sentence does not appear to provide useful guidance.

12. Appendix 2: Blow-Fill-Seal Technology, C. Batch Monitoring and Control, lines 1798-1799

The statement, "Continuous monitoring of particles can provide valuable data relative to the control of a blow-fill-seal operation" should be deleted. Continuous monitoring would not provide any more value than a well-planned system of representative monitoring. Inclusion of this sentence may inappropriately encourage the enforcement of continuous monitoring as a requirement for Blow-Fill-Seal operations.

Thank you for your consideration of these comments.

Respectfully,

Steve Bende, Ph.D.
Vice President Scientific Affairs