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October 24, 2003

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

Re: Docket No. 03D-0382, Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing.

Pfizer would like to acknowledge the effort put forth by the FDA in the publication of the Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing. We would also like to acknowledge the acceptance by the agency of the PQRI recommendations. It is recognized that a great effort has been made to clarify the issues published in the "Concept Paper". Pfizer appreciates the opportunity to provide the attached comments to further clarify and strengthen the proposed guideline.

Sincerely,

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COMMENTS ON DRAFT GUIDANCE

STERILE DRUG PRODUCTS PRODUCED BY ASEPTIC PROCESSING – CURRENT GOOD MANUFACTURING PRACTICE, August 2003

Line #	Text	Comment	Suggested Revision
238-239	"For example, a positive pressure differential of at least 12.5 Pascals (Pa) should be maintained at the interface between classified and unclassified areas."	The above sentence is unnecessarily specific and should be deleted. Area pressurization should not be considered an end in itself, but only a means to achieving directional airflow.	"Areas should have a sufficient airflow and appropriate positive pressure differential to minimize ingress of contamination from adjacent less clean areas. Appropriate positive pressure differential should be validated for each operation."
272-275	"Sterilized holding tanks and any contained liquids should be held under continuous overpressure to prevent microbial contamination".	Sterility can be maintained with other procedures, such as sterile vent filters.	"Sterilized holding tanks and any contained liquids should be held under appropriate conditions to prevent microbial contamination. The use of continuous overpressure should be considered."
277-278	"Gas filters (including vent filters) should be dry. Condensate in a gas filter can cause blockage or microbial contamination."	Some condensate is unavoidable.	"Gas filters (including vent filters) should be dry enough to permit sufficient air flow at process pressures to maintain tank and filter integrity. Condensate in a sterilizing grade membrane gas filter can cause blockage."
330-332	"Airflow velocities are measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area".	6" is an arbitrary distance. Delete "….and at a defined distance proximal to the work surface for the HEPA filters in the critical are."	"Airflow velocities are generally measured 6 inches from the filter face. These measurements can be correlated with airflow pattern studies to assure there is appropriate airflow in the critical zone.
537-539	"It is important to characterize the microbial content of each component that could be contaminated and establish appropriate acceptance limits	If a manufacturer processes components in a clean room to minimize bioburden, washes components with pyrogen free water that contains very low	"The manufacturer should have sufficient controls in place that provide barriers to microbial contamination, minimize bioburden/endotoxin formation, and provide assurance that adequate safety factors are provided by the sterilization and

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	based on information on bioburden."	levels of microorganisms, and uses validated overkill sterilization/depyrogentation processes for components, it is not necessary to have a program for routinely monitoring the microbial content of components.	depyrogenation processes that are used."
574-575	"Containers and closures should be rendered sterile and, for parenteral drug products, pyrogen-free."	The term "pyrogen-free" is not consistently used in the guidance. We need only to demonstrate a three-log endotoxin reduction for certain other components.	"Containers and closures should be rendered sterile and, for parenteral drug products, should demonstrate a three-log reduction of endotoxin"
608-610	"At minimum, the initial rinses for the washing process should employ Purified Water, USP, of minimal endotoxin content, followed by final rinse(s) with WFI for parenteral products."	As Purified Water USP has its own limits, this phrase is unnecessary.	"At minimum, the initial rinses for the washing process should employ Purified Water, USP, followed by final rinse(s) with WFI for parenteral products."
795-796	"For lyophilization operations, unsealed containers should be exposed to pressurization and partial evacuation of the chamber in a manner that simulates the process."	There is no pressurization in the lyophilizer.	"For lyophilization operations, unsealed containers should be exposed to partial evacuation of the chamber in a manner that simulates the process."
1001-1004	"Factors that can affect filter performance normally include (1) viscosity of the material to	Add surface tension in statement under (1)	"Factors that can affect filter performance normally include (1) viscosity and surface tension of the material to be filtered,…."

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	be filtered…"		
1050-1052	"For both the validation studies and routine production, use of a specified load configuration should be documented in the batch records."	It is not appropriate to document the validation studies in batch records. For routine production, the batch record can contain a reference to the specific load configuration.	"For routine production, use of a specified load configuration should be documented in the batch records."
1096-1097	"When determining which articles are most difficult to sterilize, special attention should be given to the sterilization of filters."	Clarity is needed to achieve the goal.	" For sterilization of filters, BI's and temperature probes should be placed both upstream and downstream of the filter, contacting or nearly contacting the filter media."
1131-1133	"Evaluation of sterilizer performance attributes such as equilibrium (come up) time studies should be helpful in assessing if the unit continues to operate properly."	It is not clear whether this is a requirement.	"Evaluation of sterilizer performance such as equilibrium (come up) time studies should be conducted during requalification to assess if the unit continues to operate within specified parameters."
1425-1426	"Nucleic acid-based methods are recommended for microbial identification purposes".	There are other methods, for example, fatty acid analysis	"Methods such as nucleic acid analysis or fatty acid analysis are recommended for microbial identification purposes".
1749-1751	"The classified environment surrounding BFS machinery should generally meet Class 10,000 (ISO 7) standards, but special design provisions (e.g. isolation technology) can justify an alternate classification."	This requirement (and use of the term *isolation technology*) is inconsistent with the phrase in line 1743 which says, "BFS machinery and its surrounding *barriers* should be designed to prevent potential for extraneous contamination." The phrase in	Sentence should be deleted.

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		line 1743 suitably addresses BFS equipment. The requirement for a Class 10,000 background should be dropped.	