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Division of Drug Information (HFD-240)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Docket No. 2003D-0382

The Massachusetts Public Health Biologic Laboratories (MPHBL; U.S. License 64) submits the enclosed comments regarding the FDA's Draft Guidance for Industry on "Sterile Drug Products Produced by Aseptic Processing."

The draft guidance is a significant improvement over the 1987 document and is long overdue however we believe that it requires some modifications. We would also encourage the FDA to update the guidance document more frequently than previously.

Sincerely,

C. A. Hay

Catherine A. Hay, Ph.D.
Senior Director, Regulatory Affairs
MPHBL

Docket No. 2003D-0382

Comments on the Draft Guidance for Industry on "Sterile Drug Products Produced by Aseptic Processing"

Massachusetts Public Health Biologic Laboratories

Line	Comments
137	Add a reference to USP <1116> regarding microbiological monitoring and acceptable levels.
181	FDA should cite other industry standards for air sampling like IES which may include isokinetic sampling, rather than describe specific air sampling techniques.
183-185	The FDA appears to imply that only remote counters are acceptable. We feel this is unreasonable. Portable counters should also be acceptable if the company has demonstrated that portable counters do not interfere with operations and suitably monitor the environment.
185	Correct reference to X.**E**
198-200	Rooms are usually designed for room air changes and airflows. ISO includes *either* airflow volume *or* velocity specifications therefore we suggest that the guidance does the same.
200	Is a reference from 1972 still appropriate?
202	Proper design cannot prevent air turbulence it can only minimize the turbulence. The guidance should acknowledge there could be turbulence and that the manufacturer must evaluate the impact on the aseptic operation(s).
214-215	It would appear to be unreasonable to expect no microbiological contaminants. Indeed, the USP has specifications for microbiological levels. There should also be some discussion about surface monitoring.
227	There appears to be no distinction between Class 100 hoods and Class 100 processing areas and that FDA would expect to see a Class 100 hood in a Class 10,000 area. Please clarify. We propose that if a manufacturer can demonstrate that a Class 100 hood in a Class 100,000 area maintains its Class 100 status during aseptic processing this should be considered acceptable.
238-239	Specifying specific pressure differentials is inappropriate as it is too specific and cannot address all scenarios.
248	Please provide a reference for the air change recommendation.
272-273	Why include the word "continuous"? The tank just needs to be held under pressure.
303-335	Reference industry standard(s).
326-329	Please clarify the expected frequency for the periodic monitoring of filter attributes – semi-annually as for the HEPA filter leak testing?
607	Change "cycles" to "steps" as several steps can make up a wash/rinse cycle.
615	Reference to XI.C is incorrect
615-616	Amend to include option to either test stoppers post-washing/autoclaving (each load) to demonstrate absence of endotoxin or to perform validation studies to show removal during washing procedure
809-811	Please explain what would qualify as a "manually intensive" filling line. Please

	specify whether or not a full production batch size is required or clarify what is meant by "approaching."
822-829	Please provide guidance regarding line speeds/vial sizes for the initial qualification of a line. Or clarify whether the approach suggested here applies to both initial and on-going line qualifications.
870-871	Delete the following sentence: "Incubation temperature should be maintained within 2.5°C of the target temperature." It is not necessary to specify a target temperature if the incubation temperature can be within 20-35°C. Indeed many firms incubate vials at two temperatures e.g., 20-30°C and 30-35°C and have growth promotion data to support the ranges.
877-878	Revise sentence to read: "Each media-filled unit should be examined for contamination by personnel with appropriate training." The requirement for "experience in microbiological techniques," is unnecessary as the inspectors only need to be trained to recognize growth within the units.
1020-1022	Pre-sterilization and post-use integrity testing should also be acceptable.
1027	Confirm that if the process is validated with one sterilizing filter it is acceptable to use two in order to reduce risk (i.e., a filter failing). The section does not address the impact/use of pre-filters.
1068-1071	Clarify "focus on the load areas" as opposed to validating/re-validating the complete load.
1115	Delete "as well as before and after validation runs."
1117	The vendor's D value should be acceptable for use and not need to be confirmed by the firm.
1287	It should be acceptable to identify microorganisms only when action levels are reached. What added value does the "routine" identification of microorganisms to the species level provide to any potential future investigation? Experienced microbiologists can recognize the organisms that constitute the normal flora of an establishment by their morphology.
1352	Delete the sentence: "We recommend the use of isolators to perform sterility testing." The firm should ensure that the environment is suitable for sterility testing e.g., in a Class 100 hood. The recommendation to use an isolator is unreasonable.
2055	Definition of "worst-case" does not apply to autoclaves (a lesser load would not pose the greatest chance of failure) therefore please clarify.