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Comments submitted by Millipore Corporation to FDA / CDER on draft guidance document (Docket No. 2003D-0382)

2003D-0382 C6 03 OCT 31 A9:28

"Sterile Drug Products Produced By Aseptic Processing"

We would like to draw the author's attention to certain text found in following section.

IX. Validation of Aseptic Processing and Sterilization.
B. Filtration Efficacy.

"Filtration is a common method of sterilizing drug product solutions. An appropriate sterilizing grade filter is one that reproducibly removes all microorganisms from the process stream, producing a sterile effluent. Such filters usually have a rated porosity of 0.2 micron or smaller". ***(Page 28: Section IX. Validation of Aseptic Processing and Sterilization.)***

Comment

The last sentence quoted above *"Such filters usually have a rated porosity of 0.2 micron or smaller"* should be removed from the guidance for the following reasons.

- Published data[1] (in the public domain) confirms that sterilizing grade filtration is not solely dependent on membrane pore size but rather on a number of critical parameters of which pore size is one variable. Removal of the sentence *"Such filters usually have a rated porosity of 0.2 micron or smaller"* is a first step toward decoupling sterilizing grade performance from membrane pore size ratings, allowing users and manufacturers alike to move toward a definition which is based on good science and good validation practices.

- The possibility exists that literal interpretation of this sentence could lead to a conclusion that the agency is setting an implied upper limit on the membrane pore size required to achieve sterilizing grade performance.

  - The FDA has been very clear that an appropriately conducted, worst case validation study is the only method to demonstrate robust sterilizing grade performance. In addition, FDA /CDER representatives during public presentations[2] have stressed the "Latitudes" offered within this guidance (i.e. Use of terms such as generally, appropriate and others).

- The sentence, *"Such filters usually have a rated porosity of 0.2 micron or smaller"* to be somewhat inconsistent with publicly stated positions[2] by representatives of the FDA/CDER.

- The best definition of sterilizing grade performance[3,4] is one which is driven by validation, a functional definition, where a membrane, regardless of it's pore size is challenged appropriately (e.g. *Brevundimonas diminuta* challenge study at 10^7

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cfu/cm^2 of effective filtration area) under specific worst-case process conditions. In addition we fully support the recommendation (within the guidance) to consider (as part of your risk assessment) the relevance of the challenge organism based on the environmental and process bioburden loads and identification.

- Finally, based on their definitions, the terms porosity and pore size are not interchangeable. Accordingly, these definitions should be clarified by FDA and appropriately used in ***Section IX. Validation of Aseptic Processing and Sterilization. Page 28.***

I would like to thank you in advance for your consideration in this matter. If you have any questions please feel free to contact me directly.

Yours Sincerely,

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References:

1. Kawamura et. al., "Absolute Sterilizing Grade Filtration - What is Required?" PDA Journal of Pharmaceutical Science and Technology. 54(6) 485-492.

2. Friedman, R. Presentation made to FDA/CDER Pharmaceutical Advisory Committee Meeting: October 22nd 2002.

3. Stinavage, P. "Filtration Issues in Pharmaceutical Manufacturing: Bacterial and Viral Retention."

4. PDA Journal of Pharmaceutical Science and Technology: Technical Report No. 26, Sterilizing Filtration of Liquids.

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