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November 4, 2003

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

Re: Docket 03D-0382

Dear Sir or Madam:

Thank you for the opportunity to review and comment on the proposed *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Process.*

The extensive amount of work that was performed by Mr. Friedman and his team is greatly appreciated. In general, this document was greatly improved from the "Concept Paper" provided to industry over a year ago. It is evident that careful review and assessment of the comments that were provided for the concept paper has taken place and many of these comments were incorporated into this document.

There are a few areas of this document that could still be improved. The following comments describe those areas. Each comment includes the line number of the affected paragraph.

- Title of the Document *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice.*

  Incorporation of the words Current Good Manufacturing Practice is confusing for industry. Other references in the Code of Federal Regulations require that pharmaceutical companies comply with current good manufacturing practice. By adding this wording, it tends to conflict with the subsequent statement that this is not a legally binding document. It is recommended that this wording be deleted. If it is felt that wording is required, perhaps calling the document by another title, e.g., best demonstrated practices or some other wording that does not reflect the cGMP would be better.

- Line 143: The Table for microbiological levels and the room air cleanliness classifications

  Although ISO Standards are useful in this system could you also please include the EU Annex 1 classification scheme. Most companies are global businesses and are mandated to follow this scheme.

  Microbiology is a logarithmic science and the microbiological levels established for the room classifications do not reflect this basic science.

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- Lines 172 – 178 Particulate monitoring in Critical Areas

  It would be really useful if FDA would put in some commentary on continuous monitoring particulate devices, e.g., that counts should be out of limits on some occasions, e.g., during room cleaning, whether it is acceptable to have delays on the alarms to account for opening doors, etc. If it is intended that every alarm, no matter the duration is investigated, this would place an extreme burden on industry and would also detract from the value of a continuous system.

- Line 182, the sentence ending with container-closures.

  The words "if possible" should be added to the end of this sentence since it is not always possible to sample at this location.

- Line 183, the sentence ending with each shift.

  Please clarify this sentence. I believe that you mean each production shift since typically it is not a requirement to continuously monitor.

- Lines 209-211: Videotaping of smoke studies

  Could you please clarify whether smoke studies that are videotaped can be edited? Also, if videotaped, is it mandatory that they be maintained? If so, for what duration of time should they be maintained?

- Line 244 ...frequently...

  Since frequently is defined in the European annexes, could you please define or provide an example for frequently?

- Line 393 regarding the word disinfected

  Many items are currently taken into the clean room after sanitizing with 70% IPA. Could you please clarify whether this wording was to mean sanitize or disinfect or are you expecting all items to be disinfected. Scientifically these two words are not synonymous.

- Lines 441-443 regarding use of sterile instruments.

  Recommended rewording: Between uses, instruments should be place in sterilized containers, or maintained in a way to prevent contamination, e.g., suspended on a holder in the Class 100 area.

- Lines 493 – 494: regarding the frequency of re-qualification

  This sentence is confusing for two reasons, (1) what is meant by an automated line? (2) What is the expectation for a manual system?

  The frequency is not an issue, if by automated line one does not mean you have to have a barrier or isolator system, i.e., most traditional filling/stoppering lines in use. However, if your expectation for an automated line is different, it should be defined.

In the event the system is more manual, could you please give some guidance on the frequency you would expect as a minimum?

- Line 596 regarding qualification of dry heat processes

  I think you are missing a requirement for endotoxin challenges in this section.

- Lines 611-612 regarding minimizing the time between washing and sterilizing stoppers

  This section although important, is hard to enforce when purchasing ready-to-sterilize stoppers. Perhaps it could be addressed by adding a sentence like: In the event that the time from washing to sterilization is longer, the stoppers should be maintained in a container/closure system that acts as a microbial barrier to prevent subsequent contamination.

- Line 846 regarding the use of representative isolates for testing media

  It should be noted that many environmental isolates are not hearty and are difficult to maintain. As such, procedures used to make them into "saved" cultures frequently change the characteristics of the media. Based upon this guidance, would one be cited for non-compliance when they meet the compendial requirements?

- Lines 1054-1058 Last sentence of this paragraph.

  Recommended rewording: It is important to remove the air present in a saturated steam sterilization cycle.

  The wording as written in the proposal would include air/steam mixtures where the air is an important component of the sterilization cycle.

- Line 1077 Qualification : Empty Chamber

  This type of study is generally an initial validation study, not a routine qualification study. The word qualification should be changed to validation.

- Line 1087 Validation: Loaded Chamber

  This type of study is part of the routine qualification of the vessel and the word validation should be replaced with qualification.

- Lines 1117 and 1118: regarding D-value testing

  Although I totally agree that each lot and shipment of biological indicators should be confirmed for D-value and control count, the requirement to do this for each validation study places undue burden upon industry. Data from Dr. Pflug and from studies conducted at facilities where I worked indicate that the D-value is stable for more than a year, when stored at a continuous set of temperature/pressure conditions.

- Line 1293 ... environments at frequent intervals...

  Please change the wording from frequent, to periodically. The frequency of identification and the value of identification is really a business risk, e.g., in the event of a positive growth on a media fill how much product is at risk. Companies should be allowed to evaluate the business risk to determine the frequency of identification.

- Line 1326 ...demonstrate increased accuracy....

  According to the USP, one must only show equivalent or better results. This wording does not allow for equivalent results.

- Lines 1328 – 1334 regarding Particulate Monitoring

  Please add provisions/guidance for the use of continuous monitoring systems.

- Lines 1425 and 1426 regarding nucleic acid- based methods are recommended...

  Mike Waddington of Accugenix presented some very interesting data on the ability of identification systems to be accurate and reproducible. Even nucleic acid based methods may not be accurate or reproducible. This paragraph would be strengthened by adding a sentence like the following. When comparing results to invalidate a sterility test positive, both identifications should be performed using the same methodology (type of system).

Please commend the authors of this document on the hard work they have done!

Best regards,

Jeanne Moldenhauer
Pharma Consultant