# Bayer HealthCare
## Biological Products Division

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October 21, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1601
Rockville, MD 20852

Carol M. Moore
Vice President
Worldwide Regulatory Affairs
Responsible Head/Agent
Biological Products Division

**Re: COMMENTS - Draft Guidance for Industry**
**Sterile Drug Products Produced by Aseptic Processing**
**Current Good Manufacturing Practice**

**Docket No. 03D-0382**

Dear Sir or Madam:

The purpose of this correspondence is to provide comments and suggestions regarding the draft guidance document. Ten comments are listed in table format with suggested changes in blue text.

If you have any additional questions or comments concerning this correspondence, please contact either Paul Gil at our Clayton, North Carolina facility (919-359-7146) or me.

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Sincerely,

Carol M. Moore
Vice President
Worldwide Regulatory Affairs
Responsible Head/Agent

CMM/PJG/kka
Attachment

03D-0382 C4

| Line | Current Verbiage | Suggest Change To | Comment |
|---|---|---|---|
| 202 | Proper design and control should prevent turbulence or stagnant air in the aseptic processing line or clean area. | Proper design and control should **minimize** turbulence or stagnant air in the aseptic processing line or clean area. | Turbulence in some locations (e.g. directly underneath the filling line conveyor) is unavoidable. |
| 240 | This same overpressure should be maintained between the aseptic processing room and adjacent rooms (with doors closed). | This same **differential pressure** should be maintained between the aseptic processing room and adjacent rooms (with doors closed). | The term "overpressure" could be misinterpreted to imply a sudden spike of pressure. |
| 242 | When doors are open, outward airflow should be sufficient to minimize ingress of contamination, and the time that a door can remain ajar should be strictly controlled. | When doors are open, outward airflow should be sufficient to minimize ingress of contamination, and the time that a door can remain ajar should be **minimized**. | The words "strictly controlled" are too subjective. |
| 249 | For areas of higher air cleanliness, significantly higher air change rates will provide an increased level of air purification. | For areas of higher air cleanliness, higher air change rates **are recommended**. | "Significantly" is a subjective term and should be deleted. Increasing the airflow will not necessarily increase the "level of purification" of air downstream of the filter. It will, however, provide a greater "washing" effect (less residence time) of room particles. |
| 254 | Operating conditions should be restored to established, qualified levels before reaching action levels. | Operating conditions should be restored to established, qualified levels **as soon as possible.** | Many HVAC failures do not involve gradual decay, in fact, most failures (e.g. fans, belts) are immediate and there is no built in response time. |
| 311 | For example, depending on the accuracy of the photometer, A DOP challenge should introduce the aerosol upstream of the filter in a concentration ranging from approximately 25 to 100 micrograms/ liter of air at the filter's designated airflow rating. | An appropriate challenge should be **based on the sensitivity of the aerosol photometer.** | IEST Recommended Practice CC006.2 (Testing Cleanrooms) recommends a minimum challenge of 10 micrograms/liter. This concentration is adequate for detecting leaks with most current photometers in use while minimizing the aerosol challenge the HEPA filters are exposed to. Higher concentrations would only be needed if a less sensitive instrument were used. |

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|---|---|---|---|
| 321 | A single probe reading equivalent to 0.01% of the upstream challenge should be considered as indicative of a significant leak and should result in replacement of the HEPA filter or, when appropriate, repair in a limited area. | A single probe reading **exceeding** 0.01% of the upstream challenge should be considered as indicative of a significant leak and should result in replacement of the HEPA filter or, when appropriate, repair in a limited area. | IEST Recommended Practice CC006.2 (Testing Cleanrooms), Section 6.2.1.c. states "Report all leaks exceeding the following: For a linear readout photometer (what we use), a reading greater than 0.01% of the upstream challenge aerosol concentration or as otherwise agreed." |
| 330 | 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. | Airflow velocities are measured **at defined distances proximal to the filter face** for HEPA filters in the critical area. | Measurement at 6 inches is not critical so long as the measurement is proximal and consistent. The intent should be to determine consistency and changes in velocity. Measurements at a defined distance proximal to the filter face are adequate to determine this. |
| 333 | HEPA filters should be replaced when nonuniformity of air velocity across an area of the filter is detected or airflow patterns may be adversely affected. | HEPA filters should be replaced when nonuniformity of air velocity across an area of the filter **adversely affects airflow patterns**. | Differences in velocities should be acceptable provided the airflow pattern is not affected. |
| 489 | Gowning qualification should include microbiological surface sampling of several locations on a gown (e.g., glove fingers, face mask, forearm, chest, other sites). | Gowning qualification should include microbiological surface sampling of several locations on a gown (e.g., glove fingers, facemask **or goggles**, forearm, chest, other sites). | It is difficult to take a microbiological surface sample from an operator's facemask aseptically. There is a significant potential to contaminate the sample from the sampling process itself. |