B|BRAUN

B. Braun Medical Inc.
2525 McGaw Avenue
P.O. Box 19791
Irvine, California 92623
Telephone: (949) 660-2176
Fax: (949) 660-3292

7913 '03 NOV -4 P3:19

03 November 2003

Division of Dockets Management [HFA-305]
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Submitted Electronic by E-mail to **<fdadockets@oc.fda.gov>**
Guidance Document Reference: Vol. 68 (September 5, 2003): Docket No. 03D-0382, CDER 1997112. Pages 52782-52783 [FR Doc. 03-22576]

Dear Guidance Document Manager,

Re: Review Comments on "Sterile Drug Products Produced by Aseptic Processing" Draft Guidance

B.Braun thanks the Agency for the opportunity to submit comments and suggestions on the proposed "Sterile Drug Products Produced by Aseptic Processing" guidance. B.Braun is a leading manufacturer of large and small volume parenteral drug products. B.Braun started aseptic processing with the development and approval of two of its cephalosporin drug products packaged in the B.Braun Duplex® delivery system. Two of B.Braun Duplex line products are: Cefazolin (NDA 50-779, approved 7/27/00) and Cefuroxime (NDA 50-780, approved 2/21/01). Please find enclosed our comments to the above guidance document.

The comments have been prepared based on science and our experience in aseptic process manufacturing. We hope you find the comments helpful in finalizing an aseptic processing guidance that is clear, appropriate, and consistent with current aseptic processing techniques. The comments are summarized into "Issue," "Proposal," and "Objective of Proposal," for each line or section referenced. Current texts proposed for deletion are in ~~strike through~~ and proposed new texts are <u>underlined</u>.

If you have any questions on these comments, please feel free to contact me.
Sincerely,

Sgd
Qansy Salako, Ph.D.
Director, Regulatory Affairs
E-mail: qansy.salako@bbraun.com

2003D-0382

C17

DOCUMENT	COMMENT
Lines 134-135, 146	**Issue:** Footnote "a" does not allow it up to the manufacturer to determine whether the classifications must be met under static or dynamic conditions as written in ISO 14644-4, which is recognized in the USA. **Proposed:** Delete Footnote "a". **Objective of Proposed Modification:** To bring the FDA aseptic processing guidance document into alignment with ISO 14644-4.
Line 143	**Issue:** The active microbiological action levels shown in the columns labeled "Microbiological Active Air Action Levels" and "Microbiological Settling Plates Action Levels", should not be dictated as the limits should be established based on historical microbial data. If microbiological levels are listed in Table 1, they should be modified to those listed in Table 3 of USP <1116> Microbiological Evaluation of Cleanrooms and Other Controlled Environments. **Proposed:** Delete the columns labeled "Microbiological Active Air Action Levels" and "Microbiological Settling Plates Action Levels" in Table 1 or harmonize the values listed in the "Microbiological Active Air Action Levels" with those listed in USP <1116>. **Objective of Proposed Modification:** To avoid confusion among manufacturers who currently use the levels listed in Table 3 of USP <1116>.
Line 248	**Issue:** The number of air changes per hour shown for a Class 100,000 (ISO 8) area is ≥20 per hour, but in ISO 14644-4 a range of 10-20 per hour is given for an ISO 8 area. **Proposed:** "For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve ~~at least 20~~ 10-20 air changes per hour would be typically acceptable. **Objective of Proposed Modification:** To harmonize the document with ISO 14644-4 and to avoid confusion among aseptic manufacturers.

DOCUMENT	COMMENT
Line 249	**Issue:** The sentence, "For areas of higher air cleanliness, significantly higher air change rates will provide an increased level of air purification" is ambiguous. **Proposed:** ~~For areas of higher air cleanliness, significantly higher air change rates will provide an increased level of air purification~~. In areas that are ISO 8 (Class 100,000), ISO 7 (Class 10,000), and ISO 6 (Class 1,000); the number of air changes per hour should be 10-20, 30-70, and 70-160 respectively. **Objective of Proposed Modification:** To harmonize the document with ISO 14644-4 and to avoid confusion among aseptic manufacturers.
Line 262	**Issue:** The sentence "A compressed gas should be of appropriate purity…", needs clarification by the agency. **Objective of Modification:** Enhance document clarity.
Line 348	**Issue:** The word "sterility" is misspelled. **Proposed:** ~~sterilty~~ sterility
Line 491	**Issue:** Regarding the statement, "Following an initial assessment of gowning, periodic requalification should monitor various gowning locations over a suitable period…," we believe that once an individual has passed the initial gowning and if that individual is monitored regularly (e.g. daily, each shift, etc.) throughout the year, a requalification would not be of value. Any personnel monitoring excursions during the requalification period would warrant immediate and appropriate corrective action (i.e. ban employee from entering the area until re-training and re-qualification are satisfactorily completed). If there are not any excursions for a particular individual during a requalification period, the individual is gowning satisfactorily. **Proposed:** Following an initial ~~assessment of~~ gowning qualification, ~~periodic requalification~~ routine monitoring should ~~monitor~~ include various gowning locations ~~over a suitable period~~ to ensure the consistent acceptability of aseptic gowning technique.
Line 600	**Issues:** A reference(s) should be included for the sentence, "Pyrogen on plastic containers can be generally removed by multiple WFI rinses." **Objective:** A reference(s) would provide the scientific basis this generalization.

DOCUMENT	COMMENT
Line 898	**Issue:** Regarding Footnote 9, "To assess contamination risk during initial aseptic setup (before fill), valuable information can be obtained by incubating all such units that may be normally removed", we believe that if the units that are normally discarded during set-up but in the media fill are incubated for information purposes, will a positive growth result in an information unit (normally discarded unit) count as a contaminated unit with respect to the media fill (re)qualification? **Proposed:** To assess contamination risk during initial aseptic setup (before fill), valuable information can be obtained by incubating all such units that may be normally removed. A positive growth in a vial that is normally discarded during initial setup does not result in a failing media fill run, but should lead to an immediate investigation and appropriate corrective action. **Objective of Proposal:** To clarify the agency's position regarding the impact of contaminated containers on a media fill that are normally discarded during production.
Line 805	**Issue:** The minimum run size for media fills has been historically 3,000 units. The 3,000 unit limit was based on a statistically valid justification. **Proposed:** A generally acceptable starting point for run size is in the range of ~~5,000~~ 3,000 to 10,000 units. **Objective of Proposal:** To keep a statistically valid minimum container requirement for media fills.
Line 921	**Issue:** It is not always possible to identify microorganisms to the species level. **Proposed:** If possible, t~~T~~he microorganisms should be identified to species level. **Objective of Proposal:** Many organisms have not yet been identified, which sometimes makes identification to the species level, or even the genus level, impossible.
Line 1117	**Issue:** Clarification is needed regarding how far in advance the microbial count and D-value of a biological indicator should be confirmed before a validation study. **Objective:** Enhance document clarity.

DOCUMENT	COMMENT
Line 1326	**Issue:** Historically, other suitable microbiological test methods (e.g. rapid test methods) should be allowed for use after they have been shown to be equivalent to (or better) than traditional methods. **Objective:** To allow the use of alternative equivalent methods and to be consistent with USP.
Line 1681	**Issue:** A breach of isolator integrity should lead to a decontamination cycle only if the breach could have impacted sterility in the isolator (e.g. positive pressure maintained in an isolator during a breach may not warrant a decontamination). **Proposed:** A breach of isolator integrity should lead to a decontamination cycle <u>if positive pressure was not maintained or if it is believed that the breach could have jeopardized sterility within the isolator</u>. **Objective:** Not all breaches necessarily jeopardize isolator sterility (i.e. a "mouse hole" is open to the environment, but positive pressure within the isolator maintains sterility.)
Line 1700	**Issue:** Air quality should be monitored periodically during each shift." Please clarify as to specifically which aspects of air quality (e.g. non-viable, viable, or both) are to be monitored per shift. **Objective:** Enhance document clarity.