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Parenteral Society

European Sterile Products Confederation Member

November 4, 2003

Docket Number 2003 D- 0382
Guidance For Industry
Sterile Drug Products Produced by Aseptic Processing
Current Good Manufacturing Practice

Draft Guidance

Dear Sirs,

Please find attached the co-ordinated comments from the European Sterile Products Confederation (ESPC).Please address all communications to the mail or e-mail address at the head of this letter.

Sincerely,

pp. Slagt

Dr. Gerry Prout.

2003D- 0382 C35

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Parenteral Society Comments on

Guidance for Industry

Sterile Drug Products Produced by Aseptic Processing -

Current Good Manufacturing Practice

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Introduction

The Parenteral Society is a UK based professional not for profit society with approximately 1200 members with a worldwide geographic distribution.

The comments below have been co-ordinated by the Parenteral Society, based on information received from members of the Parenteral Society and other European organisations who are members of the European Sterile Products Confederation (ESPC).

Members of ESPC are APV (Germany), R3 Nordic (Nordic Countries), A3P (France), AEFI (Spain). In total these organisations represent over 10,000 professionals working in activities related to the pharmaceutical industry.

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Comments

Comment Number	Page	Line	Comment	Proposal
1	2	22, 23, 70, 71	The text in lines 70 and 71 is superfluous in that it is already stated in lines 22 and 23 that the document refers to products produced by aseptic processing.	Delete lines 70 and lines 73 thru 78
2	3	92, 93	The sentence commencing Alterminally sterlized drug product..., is out of context. See comment 1.	Delete the sentence in lines 93 and 93
3	3	114	"In such cases" is not a defined situation	Delete "In such cases"
4	4	127, 128	The sentence starting "Design of a given area at seq. Is not clear	Replace the sentence with "Microbiological and Particulate Standards are defined in regulations and recommended guidance documents. The activities, equipment, components and products exposed must be appropriate to the types of products being processed and they should be controlled to meet class requirements
5	4	137	This line is in conflict with line 176	Replace "on a routine basis" with "whenever processing operations are being conducted
6	5	142	Table: No mention of 5 micron particles Equivalence of ISO and GMP requirements is not clear. Microbiological levels are not stated to be upper or maximum limits	The table should be re-organised to current ISO 14644-1 in first column, superseded FS 209E equivalent in second column and metric equivalent in third column
7	5	160	"preserve sterility" is incorrect	Replace "preserve sterility" with "to minimise the risk of contamination"

Comment Number	Page	Line	Comment	Proposal
8	5	172 – 176	Uses metric and imperial units	Use only S1 units, replace micron with micrometer throughout the document
9	5	176	The sentence on this line is out of context and misleading	Delete This level of air cleanliness is also known as class 100 (ISO 5)
10	6	196	Laminar flow is not defined in ISO 14644-1	Replace Laminar flow with unidirectional flow for consistency with ISO 14644
11	7	238	The use of 12.5 pascal is inappropriate Harmonization with the EU 10 – 15pa	Harmonise with EU 10 – 15 pa
12	7	247 - 250	These lines can be misinterpreted	Replace the sentence in lines 249 and 250 with "For areas of higher cleanliness, significantly higher air change rates are likely to be required to achieve the required levels of "in-operation" air cleanliness
13	7	258	D. Air Filtration is too restrictive	Replace "Air Filtration" with "Filtration of Gases"
14	8	272	The sentence commencing "Sterilized holding tanks ---. Is restrictive	Replace with "Sterilized vessels and contained liquids should be maintained under conditions which minimise the possibility of microbial contamination
15	8	280	It is not common practice to test filters during processing as this increases manipulations	Replace "and periodically thereafter", with at "end of use" Delete (e.g. including at end of use)
16	8	283	High Efficiency Particulate Air (HEPA) is meaningless	Replace with High Efficiency Particulate Air Filters (HEPA filters)

Comment Number	Page	Line	Comment	Proposal
17	8	288	Integrity testing of HEPA filters in unidirectional air work stations and critical areas should be carried out twice per year. HEPA filters in other locations should be "in situ" tested once per year.	
18	8	297	Diocytyl phthalate is carcinogenic	Delete diocytyl phthalate (DOP)
19	9	330	"can have an effect" is ambiguous	Insert " adverse" between "an" and "effect"
20	10	344	The first sentence is unclear as to its meaning	Replace with "Aseptic processes must be designed, configured and operated to minimise exposure of sterile articles to potential contamination
21	11	365	"prefastened" is not a recognised industry word	Use "preassembled" to replace prefastened
22	11	374	"---- provide class 100 (ISO 5)" is not adequately descriptive	Replace with "critical area level"
23	12	403	The sentence "With rare exceptions, drains are not considered appropriate for classified area of the aseptic processing facility" is not correct.	Replace the sentence with "With rare exceptions, open drains are not appropriate for critical areas. Where drainage is required outside the critical area it is preferable for the waste to be piped to a drain in a less sensitive technical area
24	13	422	The process should not only be well designed but also operated and maintained	Replace existing with "A well designed, operated and maintained aseptic process minimises personnel intervention"
25	14	443	This line/sentence is redundant	Delete sentence
26	15	475	"Only personnel who have been qualified" is incorrect	Replace with "Only personnel who are currently qualified-----"

Comment Number	Page	Line	Comment	Proposal
27	15	477	A gown will not "prevent" contamination	Replace "prevent" with "minimise"
28	15	493/494	This sentence is not clear	Delete semi-annual. Current industry practice is annual requalification
29	17	564 - 566	These lines are too cumbersome	Replace with "Parenteral products are intended to be non pyrogenic. Any component failing to meet defined endotoxial limits must be rejected
30	24	805	ISO 13408 requirements should be used in place of current text	Refer to ISO 13408
31	36	1292	The words "species" and "genus" appear to be reversed	Replace with "-----the program should require genus (or where appropriate, species) ------
32	36	1309	The meaning of the sentence is not clear	Start sentence with "The testing of incoming lots -----
33	46	1596	Replace wg with pascal	Use S1 units throughout
34	38 – 42	1338 - 1499	The section X1 Sterility Testing is redundant	Delete section. Add one line. For details of sterility testing refer to current United States Pharmacopoeia
35	45, 48	1547, 1556, 1682	Text is not clear	Replace with "All breaches of integrity should be investigated. A risk analysis should be conducted if product has or may have been compromised
36	46	1587 1648	"Sterilization" is inappropriate in this sentence "Sterilant" is inappropriate	Replace "sterilization" with the word "decontamination" Replace "sterilant" with "decontaminant"
37	59	2021, 2022	Laminar flow is not a correct term in this context and is not used in the text.	Delete the definition