



PDA Global Headquarters

3 Bethesda Metro Center
Suite 1500
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

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and Technology*:
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University of Iowa

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Mrs. Sabine Atzor
European Commission
Enterprise DG, Pharmaceuticals
Rue de Genève, 1
1049 Brussels
Belgium

Mr. David Cockburn
European Medicines Evaluation Agency
7 Westferry Circus
London E14 4HB
United Kingdom

Dear Mrs. Atzor and Mr. Cockburn:

PDA is pleased to provide these comments on GMP Annex 1: Proposals for amendment to the environmental classification table for particles and associated text, amendments to section 42 concerning acceptance criteria for media simulations, amendment to section 52 concerning bio-burden monitoring and additional guidance in section 88 on the sealing of vials. PDA is an international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical manufacturing and quality. Our comments were prepared by a committee of 16 experts in this field from 15 different companies or consultancies representing 7 different countries including all three major pharmaceutical markets.

PDA understands the necessity and value of guidance documents such as Annex 1: Manufacture of Sterile Medicinal Products. Such guidance documents provide a valuable role in assisting both the regulated industry and regulatory agencies in their compliance responsibilities. To assist in a developing guidance document that represents current Good Manufacturing Practice utilising the best scientific information available and that incorporates internationally accepted GMP the PDA is pleased to offer these comments. The key points that we would like to make are:

- We offer clearer text associated with the environmental classification table in Clause 4. We have revised the table to be more aligned with EN ISO 14644-1, which is the internationally accepted standard for non-viable particle classification. We have revised the note under the table to reflect industry practice, e.g., trend analysis, and to incorporate the guidance provided under Clause 6.
- We agree with the intent of revised Clause 47 to harmonise process simulation tests (media fills) with the equivalent FDA guidance document. We have slightly modified the section to more closely align it with the FDA guidance document. We have suggested removing the requirement for performing media fills per shift and

replaced it with the requirement that each person involved in aseptic processing should participate in at least one media fill per year. This is to address the need for each person, as part of their ongoing training/qualification requirements, to participate in at least one media fill and to address the point that with modern manufacturing practices it is becoming increasingly difficult to define a shift.

- We have suggested an adjustment to new Clause 57 to take account of the improved sterility assurance provided by the practice of using duplicate in-line sterilising grade filters for solution filling operations. When using duplicate in-line filters we believe it appropriate that the bioburden might be monitored only at suitable scheduled intervals.
- We have provided revised guidance on appropriate environmental conditions for the handling of lyophilisation vials between partial stoppering and final sealing. The new Clause 93 received the largest number of comments with all disagreeing with the requirement that: "Partially stoppered freeze dried vials should be maintained under Grade A conditions at all times, from the time of partial stoppering to capping". We offer a revised Clause 93 that represents proven good aseptic practice that is harmonised with other internationally accepted cGMP guidance documents.
- In general, we offer comments to more align Annex 1 with EN ISO 14644 and internationally accepted aseptic practice and GMP. We offer editorial comments to improve the continuity and clarity of some text.

Attached please find a document that provides a Summary of PDA's Comments, as well as a second document where we have incorporated member comments into PDA Suggested Text for Annex 1.

PDA appreciates the work EMEA has put into revising Annex 1 and we offer these comments towards a joint effort for developing a scientifically sound GMP guidance document.

We would be pleased to discuss these comments with you at your convenience.

If I can be of further assistance, please feel free to contact me.

Yours sincerely,



Georg Roessling, PhD
Senior Vice President
Europe Operations, PDA