PDA Commentary on:

EU Guide to Good Manufacturing Practice,
Annex on the Manufacture of Sterile Medicinal Products, (Draft 4, III/5805/94, 19 June 1995)

Explanatory Note:

In June 1995 the EU published a revised version of the subject Annex for international commentary. An international working group of PDA expert volunteers worked under short time frames to prepare extensive comments on the revisions to the Annex, as well as the existing text. Comments were submitted to the EU on November 21, 1995, and forwarded to FDA officials on January 23, 1996, suggesting the possibility of harmonization.

These comments represent the first PDA commentary on non-USA regulatory guidance.

In June 1996 the EU Working Party on Control of Medicines and Inspections conducted its final review of comments and prepared a final version of the Annex for adoption.

PDA Staff Contact: James C. Lyda, x121
July 1996

November 21, 1995

Philip Meyer
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Dear Dr. Meyer,

The Parenteral Drug Association is a non-profit international association founded for the purpose of education and technical information exchange in the areas of development, manufacturing and quality assurance for pharmaceuticals, biopharmaceuticals and related health care products. Our 7,200 worldwide members include scientists and technical representatives of pharmaceutical manufacturers including multinationals, academia, government, and suppliers of equipment and services to the pharmaceutical industry.

Enclosed are PDA's comments on the proposed revision of the EU Guide to Good Manufacturing Practice Annex on the Manufacture of Sterile Medicinal Products, or 'Annex.' Our members will be affected by the Annex, and we appreciate the opportunity to provide comments before the Annex is finalized. The comments were prepared by a special task group appointed by PDA, consisting of industry experts in the field of sterile medicinal manufacturing from Europe, the United States of America and Japan.

We have not limited our comments to the new text and tables in the proposed revision, but have also provided comments on existing text in the current version. We believe that this is appropriate because technology obviously changes over time, and the working party may want to consider further modifications to the existing text.

We believe that the process of revising the Annex provides an excellent opportunity to consider harmonization of European and American sterile products requirements. There is no other harmonizing effort at present, and significant differences exist among documents being developed in Europe and the USA. Unless a substantive harmonization takes place, the industry will have difficulty in complying with different requirements in different regions. We are sending a copy of these comments to the Food and Drug Administration and the United States Pharmacopeia with a recommendation that the US regulatory authorities participate in such harmonization. PDA would be glad to assist in this effort in any way that would be productive.

In preparing these comments, our goal was to be constructive, not simply critical, and I urge you to view the comments in that vein. Again, we appreciate the opportunity, and please contact me at any time if you have questions or require any clarification.

Sincerely,

Edmund M. Fry

cc: Theo Berg, Netherlands Health Care Inspectorate
John Turner, Medicines Control Agency

PDA Commentary
EU Guide to Good Manufacturing Practice
Annex on the Manufacture of
Sterile Medicinal Products
(Draft 4, III/5805/94, 19 June 1995)

Introduction

Following is PDA's consensus commentary on the proposed revision of the *EU Guide to Good Manufacturing Practice, Annex on the Manufacture of Sterile Medicinal Products*, or 'Annex.' Our comments are divided into three parts:

> The Rationale for Harmonization - due to regulatory demands and industry globalization, PDA urges the European Union (EU) and the United States (US) to come to agreement on the over-arching requirements for sterile medicinal manufacturing
>
> Major Technical and Regulatory Issues - the most critical issues for debate and resolution, regardless of the prospects for formal harmonization efforts
>
> Additional Issues - topics which do not carry the international regulatory implications of the preceding section, e.g. technical clarifications, terminology, etc.

While the comments focus on new text and tables found in the proposed revision, attention was also given to text in the current version of the Annex. We feel this is appropriate as technology and concepts change over time, and there is always room for updating and clarification.

All comments on specific text follow the order and paragraph numbering of the Annex. Revised wording is usually shown in italics.

I. The Rationale for Harmonization

PDA believes the time has come for the EU and the US regulatory authorities, in consultation with the affected industries, to harmonize the fundamental manufacturing and registration requirements for sterile medicinal products.

- **Sterile medicinals are rigorously regulated** - Sterile medicinals have been the subject of rules and requirements which, while fundamentally similar (we all demand safety, efficacy and purity in our products), vary in the specific requirements and expectations of the regional regulators. Requirements and guidance include regional and World Health Organization (WHO) GMPs, pharmacopeia's and emerging international standards. In the US, sterile medicinals are subject to the unique FDA requirement for submission of validation data regarding the sterilization process before approval of the marketing application.[1]

- **Globalization continues** - Globalization of industry sourcing and markets make it increasingly wasteful for manufacturers to address sterility requirements peculiar to a specific jurisdiction. This is especially true when there is valid scientific debate on the public health and safety value of some requirements.

- **No other forum** - Sterile medicinal issues will probably not be addressed by the ICH.[2] This is consistent with the ICH goal of focusing on registration.

- **The opportunity for international harmonization of GMP and compendial requirements for sterile medicinal products** - The need for harmonization exists and the lack of an appropriate forum has been lamented by both industry and regulatory observers. The proposed revision of the Annex provides the opportunity to begin this process.

ICH has shown that harmonization will not be a simple or rapid process, nor can it cover all technical issues. Yet it also teaches us that even difficult technical issues can be the subject of a scientific consensus building process. Sterility assurance for medicinals is amenable to such a process. PDA is prepared to support that effort.

II. Major technical and regulatory issues

Following are the major issues for harmonization based on regulatory impact and potential for scientific consensus.

General

1. Recommendation: Clarify the use of 'airlocks.'

Rationale: True airlocks need only be used for what is frequently referred to as the 'sterile core,' and not for preparation areas. Also, the wording might be interpreted as requiring separate airlocks for people and materials, which is not necessary. Where separate airlocks may be needed for a specific situation, it should be left to the manufacturer to make that determination.

3. Recommendation 1 on table, 'Environmental grades for clean zones/areas': Reconsider the four tiered grading system (Grades A through D) in terms of harmonization with three tiered grading systems used in other parts of the world.

Rationale: The four tiered system is inconsistent with current practice in the USA and Japan and is confusing. The viable and non-viable classification tables included in Attachment 1 point to the dissimilarities among US, USP, and EU requirements. Use of a harmonized three tiered system would eliminate confusion without compromising product quality and would significantly reduce facility, registration, and compliance costs.

Recommendation 2 on table, 'Environmental grades for clean zones/areas': Delete reference to 5.0 μm particle size.

Rationale: The 5.0 μm particles are not normally monitored by medicinal manufacturers in most of the world. The FDA aseptic processing guideline references only 0.5 μm particle size. There is industry consensus that monitoring only 0.5 μm particles provides adequate data on air particulate quality for medicinal products.

Recommendation on table 'Examples of operations to be carried out in the various grades': Delete table and insert wording similar to Note 15 in ISO/CD 13408.3, 'The specification of air quality in each zone depends on the nature of the operation being carried out.'[3]

Rationale: The FDA aseptic processing guideline gives examples for some operations to be conducted in 'Class 100' conditions, but does not attempt to give guidance for less critical operations. The aseptic processing operations in use by the industry are too diverse to be categorized in this manner, and will likely become more so in the future.

5. Recommendation: Add following sentence to 2nd paragraph: 'Routine environmental monitoring for anaerobes is not required.'

Rationale: The literature and extensive experience suggest routine monitoring for anaerobes is unnecessary.[4][5]

Recommendation on table 'Guidance values for microbiological monitoring of clean rooms in operation': This new table should be removed from the text, or put into abeyance pending future discussion.

Rationale: The quantification of small numbers of viable microorganisms is problematic as there are today no scientific rationales or standard methodologies upon which to base such quantification. Each manufacturer should be responsible for establishing its own microbial levels based on historical data, individual facility operations and specific product considerations.

> NOTE There is need for joint industry, regulatory and compendial discussions on these issues in a forum such as the upcoming USP Open Conference on Microbiological Compendial Issues.[6] A similar European forum is needed. We propose that environmental monitoring action levels be harmonized in the EU GMPs, USP and other compendia.

Isolator technology

> NOTE For purposes of this commentary only, isolators are considered to be enclosures that exchange air with the surrounding environment only through HEPA filters, are sterilized using validated sterilization procedures, and allow entry of materials through specialized transfer devices which maintain the microbial integrity of the sterilized isolator.

6. Recommendation: Revise this paragraph to reflect the improvement isolation systems offer:

'The *proper* utilisation of isolator technology to minimise human interventions in processing areas *will* produce a significant decrease in the risk of microbiological contamination from the environment of aseptically manufactured products. When isolators are properly used *many* of the principles in this annex *may not* apply, particularly those relating to air quality and monitoring. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices. The air classification of the background environment depends on the design of the isolator and its application.'

Rationale: Isolation technology is still in a developmental phase for industrial application. As originally written, this section requires isolation systems to comply with the Annex regardless of the technical need. The proposed revision confirms the benefit to be gained from proper application of isolator technology, and recognizes that traditional monitoring may not be useful or even desirable. The rewrite suggests that background environment is dependent on the design, operation and application of the isolator system. This will allow future determinations, based on

accumulated scientific evidence, of the level of monitoring and the type of background environment required for these systems.

> NOTE The MCA and FDA have approved an industrial isolation system with a controlled but not classified background, suggesting that a generic requirement for background is not necessary.[7]

7. Recommendation: Line 2: Delete the word 'sanitisation', to read '...for example, sterilsation of the isolator...'

Rationale: Consistent with the description of isolator offered above.

Blow/fill/seal technology

9. Recommendation: Revise this paragraph as follows:

'Blow/fill/seal units are special purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. When this equipment is *properly* used *many* of the principles in this annex *may not* apply. Because...'

Rationale: Same as preceding comments regarding isolator technology. As revised, the sentence allows for technological progress over time. The reference to absolute barrier technology, which is technically debatable, has been deleted.

Terminally sterilized products, 10., and
Aseptic preparations, 11.

Recommendation: Delete and/or revise most of these two paragraphs.

Rationale: Consistent with our comments on the second table in part 3.

Sterilisation

54 et al. Recommendation and Comment: We found inconsistent and somewhat unclear guidance in several parts of the text covering sterilization processes. These observations are described in detail under the following section 'Additional Issues.'

III. Additional Issues

General

3. Grade A, paragraph 4: The listed air flow velocities in the 3rd sentence should be described as 'nominal.' As written, they might be interpreted as absolutes. Many companies use different specifications. This change will be consistent with the FDA aseptic guideline.

3. Add statement to this section regarding air temperature and humidity similar to ISO/CD 13408.3, part 9.1.1: 'Temperature and humidity levels shall be specified, controlled and maintained to assure employee comfort while maintaining product attributes as this has a direct impact on aseptic techniques and the potential level of contamination.'

The reference to USA Federal Standard 209E following the environmental grade table needs correction. 209E uses the metric measurements and terminology such as M1, M2, etc. Previous versions of the standard use Class 100, etc.

4. There seem to be missing words from the first sentence. Environment is misspelled on line 2.

5. Paragraph 2, 1st sentence, line one: Change 'should' to 'may.' Sentence 4, Line 5: Delete '...immediately after operation,' as there are many approaches to such monitoring, including during operation.

Terminally sterilized products

10. Second paragraph: Revise as, 'Filling of products for terminal sterilisation should be done in *an environment that minimizes the risk of ingress of microorganisms and endotoxin materials*.'

Personnel

18. Rewrite sentence as, 'Wristwatches, jewelry and cosmetics should not be worn in aseptic areas.'

19. Grade B, line 2, revise as, '...a face mask and goggles should be worn...' This is preferred aseptic attire.

Premises

25. Revise as, 'Pipes, ducts and *other utilities* should be installed so that they to not create recesses and *unsealed openings and other surfaces* which are difficult to clean.'

26. Revise first sentence, 'Sinks and drains should be *prohibited from Grade A areas*.' Revise 2nd sentence, '*In other areas* they should be designed,...' Delete last sentence; open channels are undesirable.

29. Revise 2nd sentence to read, 'Adjacent areas of different grades should have a *suitable pressure differential*,' deleting the reference to the 15 pascals. This paragraph should be relocated to part 3 since it relates to room air quality.

Equipment

36. Sentence 1, line 2: Add, '*and validated*' after 'maintained.'

Sentence 3, last line: Delete '...a temperature above 70^0C.' and replace with '*..an elevated temperature, for example 70^0C, that is demonstrated to prevent growth of indigenous microorganisms*.'

Sanitation

37. Sentence 2, line 1: Insert '...and disinfected...' after 'They should be cleaned...'. Delete 'frequently' in same line. Cleaning will be done according to the written programme.

Sentence 3: Rotation of disinfectants is a controversial and unresolved issue. We suggest adoption of wording from ISO/CD 13408.3, part 11.1.8, '...rotating disinfectants should be considered due to potential changes in environmental flora/isolates.'

Last sentence: Replace with wording from ISO/CD 13408.3, part 11.3.1, 'The effectiveness of cleaning and disinfection shall be determined as part of an overall environmental monitoring programme.' The development of 'resistant strains in aseptic areas' to disinfectants has not been demonstrated.

38. Delete reference to detergents in first and last sentences. Revise last sentence as, 'Disinfectants used in aseptic areas *should be free of microbiological contamination*,' which adopts wording from ISO/CD 13488.3, part 11.1.5.

Processing

41. Revise opening of sentence to read, 'Preparations of *viable microorganism* origin should not be made...' if, in fact, this is the intent of this sentence.

42. Sentence 1: Revise as, 'Validation of aseptic processing should include simulating the process...'

Sentence 4, line 5: Replace first word 'Validation...' with '*Process simulation*...'

Sentence 5, line 7: Delete '...statistically...' This is unclear and opens a difficult debate on the use of statistics in media fills.

Revise last sentence to read, 'The contamination *rate* should be less than 0.1% with 95% confidence level.'

44. Move this paragraph to 36, as it fits more closely the information in that section.

49. Line 2: Replace '...as short as possible' with '*minimized*,' which we believe is the intent of this guidance.

50. Sentence 1, line 2: Replace '...as short as possible' with '*minimized*,' which we again believe is the intent of this guidance.

53. Revise sentence to read, 'The efficacy of any new procedure should be validated, and the validation *verified at scheduled intervals, based on performance history,* or when any significant change is ...'

Sterilization

55. Sentence 1, line 3: End sentence after 'demonstrated,' deleting '...by thermometric means...' This is a general paragraph on sterilization validation and not limited to heat.

Reword sentence 2, 'This work should be *verified at scheduled intervals, based on performance history*, and whenever significant ....' This wording more accurately describes current industry practice.

56. We became confused by the intent of this sentence, and suggest it could be deleted without loss.

57. Line 1: Delete 'only.'

58. Last sentence, line 5: End sentence after '...a sterilisation process.' Delete the rest of this sentence as it is unnecessary.

Sterilisation by heat

59. This section does not recognize the advances made in measurement technology in recent years. There is no reason to have load probes provided the sterilizer and process are properly validated.

60. This section does not provide for advances in sterilization technology including process design using F_0 or F_H concepts (e.g., inclusion of come up and come down times) and tunnel sterilization.

It would be preferable to say, 'Sterilization cycles should be validated to the minimum acceptable sterility assurance level.'

Moist heat

61. This section suggests cooling water should be sterile. We recommend revision, 'Any cooling fluid or gas in contact with the product should be *of a low, controlled microbiological limit for which closure system integrity has been validated*.'

62. Sentence 5, line 6: Delete last of sentence '...during the sterilisation period.' and replace with '...*before the release of the product*.'

63. Sentence 2, line 4: Revise to read, 'All parts of the load should be in contact with the *sterilizing agent*...'

Dry heat

65. Sentence 2, line 3: Change 'bacteria retaining' to 'HEPA.'

Sterilisation by radiation

66. Delete last sentence. Ultraviolet irradiation is now being used successfully for some applications.

67. Paragraph 2. Delete 'only' from first sentence to read, 'Microbiological indicators may be used as an additional control.' Delete last sentence which is record keeping guidance.

70. Delete or Clarify.

71 - 77. Change title of this section to 'Sterilisation with *gas*'

Filtration of medicinal products which cannot be sterilised in their final container

78. Line 2: Revise sentence to read, 'With regard to methods currently available, *terminal* sterilisation is to be preferred.' This wording preserves the desirability of a terminal process but does not restrict the choice of method.

83. Add the phrase '...*beyond established limits*' to end the sentence.

Quality control

87. Reword sentence as, 'Parametric release may be used where authorized.' This deletes wording which suggested special attention to the process when using parametric release. Processes should

be controlled the same whether using sterility testing or parametric release. Also, it would be very helpful if the Annex could provide a reference for the definition and EU policy on parametric release.

90. Sentence 1, line 1: Revise to read, 'For injectable products, water *should be monitored* ....according to the *appropriate pharmacopeial monograph*.'

PDA extends thanks to the task force which worked many hours to construct the comments:

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[1] Guideline for submitting documentation for sterilization process validation in applications for human and veterinary drug products, December 3, 1993, Food and Drug Administraton, CDER and CVM [FR 58(231) 63996

[2] International Conference on the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

[3] International Organization for Standardization, ISO/CD 13408.3, Aseptic processing of health care products (ISO/TC 198 N272), 12 June 1995.

[4] Sterile Pharmaceutical Manufacturing, Applications for the 1990's, Vol 2, Interpharm Press, 1991, Chapter 5, "Environmental Monitoring: Regulatory Issues," p 169.

[5] Abdou, M.A.F., "Determination of airborne microorganisms in a pharmaceutical plant using standard, elective and selective culture media," *Pharmaceutical Technology* 4(11):93, 1980.

[6] USP Open conference, Microbiological Compendial Issues, January 10-13, 1996.

[7] *PDA Letter*, 'Advanced Barrier Technology Conference: Regulatory and Technical Highlights' February 1995, Vol.XXXI, No. 2, p6