AKZO NOBEL Organon Inc.

November 5, 2003

CONFIDENTIAL

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SUBJECT: Docket No. 2003D-0382
Comments on Draft Guidance for Industry: Sterile Drug Products
Produced by Aseptic Processing – Current Good Manufacturing Practice

Dear Sir/Madam:

Reference is made to the FDA Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. Technical and Regulatory CMC staff from N.V. Organon, Oss, The Netherlands and Organon USA Inc., West Orange and Roseland, NJ have reviewed this document. We believe that this guidance provides information that, for the most part, will benefit the pharmaceutical industry and the patients served by the industry by clarifying the expectations of FDA regarding the GMP aspects of sterile drug products manufactured using aseptic processing. However, we note that there are sections of this guidance that contain statements which we believe should be corrected, as well as some which could be clarified and expanded, particularly to include concepts and practices that are employed internationally.

Therefore, we respectfully submit our comments regarding the draft guidance for your review and consideration. They are presented in tabular format as an attachment to this correspondence.

Should you have questions regarding these comments or have suggestions as to how we can assist in the process, please do not hesitate to contact the undersigned by phone at 973-325-4830. We welcome the opportunity to work with the Agency to ultimately make this guidance more useful to all concerned parties.

Sincerely,

Thomas L. Pituk

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Senior Director, Regulatory Affairs

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TLP/cjw

Sent via Federal Express Airbill No. 840760554324

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Organon Comments
Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice
Docket No. 2003D-0382

Comment Number	Line # Section/Title	Comment/Recommendation for Revision	Background/Rationale for Comment
1	Line 142 IV. Buildings and Facilities	Table 1 should be revised to reflect particulate and microbiological values harmonized with ISO standards.	We believe this would be a good opportunity to harmonize Air Classifications with the relevant ISO standards. EU is already moving toward such standardization.
2	Lines 249-250 IV.C Clean Area Separation	We suggest deleting that sentence and adding the following: It is recommended to evaluate the performance of the air handling system by the use of recovery time measurement (see ISO 14644 for a description of a method).	We believe that particle recovery time measurement yields data that better describe the efficiency of the process.
3	Lines 297-298 IV.D.2 Air Filtration – High-Efficiency Particulate Air (HEPA)	We suggest revising that sentence as follows: Dioctylphthalate (DOP), Poly-alpha-olefin (PAO) and DiEthylHexylSebacate (DEHS) are examples...etc.	DEHS is another aerosol used for this purpose. In some regions of the world, DOP is suspected to be carcinogenic. We recommend that FDA consider deleting reference to DOP entirely, as the other alternatives already listed may be preferable to using a possible carcinogen.
4	Line 555 VI.A Components	Add "in water" after "insoluble"	
5	Line 761 IX.A.2 Frequency and Number of Runs	Add "significant" before "change"	

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6	Line 878 IX.A.8 Incubation and Examination of Media-Filled Units	Change ""microbiological technique" to "visual inspection"	We believe that it is more useful for the examination of the media-filled units to be performed by personnel with expertise in visual inspection of parenterals. Once potentially contaminated units are identified by these personnel, those units can be segregated and tested for growth by those experienced in microbiological techniques.
7	Lines 942-944 IX.A.9 Interpretation of Test Results	We suggest revising this section to conform to the recommendations provided in ISO 13408, Part 1.	ISO criteria do allow for an increase in the number of contaminated units when a significantly higher number of units are used for media fill.
8	Lines 1020-1021 IX.B Filtration Efficacy	We suggest changing "Normally" to "For some processes"	We do not agree that integrity testing of the filter prior to processing is the routine procedure. We believe that this would depend on the specific process.
9	Line 1027 IX.B Filtration Efficacy	We suggest deletion of this sentence.	We do not agree that using sterilization-grade filters in series is a common practice. The filter arrangement generally, and whether filters are used in series specifically, is a function of the specific process.
10	Lines 1117-1118 IX.C.1 Equipment Controls and Instrument Calibration	We suggest deletion of this sentence.	Commercially available biological indicators are provided with certification of the D-Value by the manufacturers. Therefore, reconfirmation of the D-Value is not necessary.
11	Lines 1292-	We suggest that rather than recommending	We agree that the accuracy and precision

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	1295 X.B Microbiological Media and Identification	the use of rapid genotypic methods at this time, this sentence should be revised to indicate that the use of rapid genotypic methods will increase as the available databases expand.	of these methods offer an improvement over the biochemical and phenotypic techniques, but their usefulness is limited by the available databases. Until these databases are expanded, we believe that the current biochemical and phenotypic techniques are still the methods of choice for routine methods of identification. Genotypic methods should be considered as additional methods at this time rather than as the standard approach.
12	Lines 1509-1510 XII. Batch Record Review	The guidance states that "All in-process data must be included with the batch record documentation in accordance with section 211.188." We suggest revising that sentence to indicate that the relevant in-process data should be readily available for review, as needed, as part of the batch release process.	While we agree that all in-process data should be available for review as needed, we disagree that these data should all be included in the batch records. This is a tremendous volume of data that can not be integrated easily into the batch record system. We believe that if systems currently in place for handling, storage and retrieval of these data are shown to be efficient and effective, then inclusion of these data in the batch records is not necessary and does not provide added value to assurance of product quality.
13	Lines 1532-1713 Appendix 1	We suggest that this Appendix be revised to contain more current information, as provided by more recent guidelines on this topic.	We note that the Appendix contains information that is not current relative to more recently published information on this topic. For example, the ISPE Guideline, Volume 3, Sterile Manufacturing Facilities, contains more relevant information on design requirements for

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			isolators.
14	Lines 1534-1535 Appendix 1	We suggest that this sentence be revised to: Aseptic processing using isolation systems separates the external cleanroom environment from the aseptic processing line.	Using isolators does not in itself necessarily minimize the extent of personnel involvement. Rather it provides segregation of (portions of) the process from the surrounding environment. Therefore, linking the use of isolation systems with an absolute reduction of personnel involvement is not valid.
15	Lines 1547-1548 Appendix 1 A. Maintenance 1. General	We suggest that this sentence is too detailed for inclusion in this section and should be deleted.	It is understood that all components of an isolator basically "leak;" therefore, unless FDA defines "significant breach of integrity," indicating certain specific components does not provide added value to this section.
16	Lines 1560-1562 Appendix 1 A.2 Glove Integrity	We believe that "No-Glove Isolators" should be addressed in this section.	We believe that the starting point in the process of designing isolators should be "no human intervention" and, hence, no gloves would be involved.
17	Line 1566 Appendix 1 A.2 Glove Integrity	We suggest that "and the operator should also wear a second pair of thin gloves" be deleted.	The level of detail regarding specific solutions for maintaining glove integrity does not seem to be appropriate for this type of document. We believe it would be more valuable if the focus of this section is on isolator design criteria.
18	Lines 1568-1616 Appendix 1 B. Design	We suggest revising this section to reflect current documents on this topic.	There has been extensive discussion on isolators among various bodies and the industry, and various organizations (e.g., PICS, PDA and ISPE) have issued documents on this topic. We believe that

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			this section of the guidance should be revised to be in line with those documents.
19	Lines 1587-1588 Appendix 1 B.2 Materials of Construction	We suggest changing "sterilization" to "sanitization"	Isolators are not sterilized, but rather they are sanitized; therefore, ability to sanitize should be one of the criteria for selecting construction materials.
20	Lines 1585-1589 Appendix 1 B.2 Materials of Construction	We suggest deleting this section.	This section does not define the boundaries of isolators, which would include all of the technology components as well as the structural components. Therefore, this section does not provide added value.
21	Lines 1591-1607 Appendix 1 B.3 Pressure Differential	We suggest revising this section to reflect the conditions for ISO 5/Cleanroom 100 classification.	We believe that this section should address the importance of maintaining in an isolator in order to meet the air cleanliness classification of IS) 5/Cleanroom 100 classification. The current paragraph as written should not be part of this guidance.
22	Lines 1639-1640 Appendix 1 C.2 Discharge	We suggest that this section be clarified to delete "at this location" from this sentence.	Air pressure is expected to be essentially uniform throughout an isolator. Consequently, any change in pressure would result in the same value regardless of where the measurement is taken. As long as sufficient overpressure is maintained, isolation is maintained. Based on this, pressure monitoring is performed in a single location in the isolator. It is not necessary to measure pressure near the mousehole specifically.