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Docket No. 2003D-0382
Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing

Merck & Co., Inc. is a leading worldwide, human health product company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many of the important pharmaceutical products on the market today.

The Food and Drug Administration (FDA) has provided as Draft Guidance, "*Sterile Drug Products Produced by Aseptic Processing: Current Good Manufacturing Practice"* to enhance compliance in the area of sterile drug manufacture by describing procedures and practices to help manufacturers of sterile drug products meet cGMP requirements. This guidance updates and clarifies the 1987 guidance and complements the 1994 Guidance "Guideline for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".

Merck strongly supports the development of this draft guidance and applauds the Agency for its efforts. We also encourage international harmonization with respect to aseptic processing and have noted in our comments some areas where harmonization may be fostered. Additional areas of comment provide examples to strengthen consistency of terminology. We also support FDA's allowing manufacturers to determine, using sound science and based on the principles described herein, alternative approaches for their aseptic processing.

Merck has vast experience with the manufacturing of parenterals and hence are very well qualified to comment on this draft guidance. Merck has completed a thorough evaluation of the subject guidance and have organized our comments into three distinct areas: General Discussion/Recommendations, Clarifications and Other Comments.

General Discussion/Recommendations

1. Several opportunities for this FDA guidance to be harmonized with European GMP requirements, as included in Annex 1, appeared to have been missed. The creation of a unified global aseptic standard is both feasible and necessary, and should be considered. The following ten topics in the guidance appear to be in direct conflict with EU requirements and should be re-visited:

- Area classification (e.g. US Class 100/ISO 5 vs. EU Grade A)
- Static/dynamic testing (static required in EU, dynamic in the US)
- Five micron particle requirement (5 micron particle monitoring required in EU but not in US)
- Cubic meter measurement (Volume requirement explicit in EU, but not in US)
- Requirements for unidirectional flow (Difference in philosophy regarding provision of unidirectional flow)
- Isolator background requirement (EU: Grade D, US Class 100,000 – Grade C equivalent in dynamic condition)
- Blow/fill/seal background and critical zone monitoring requirement (EU background Grade C, US background Class 10,000 – Grade B equivalent in dynamic condition. Dynamic viable monitoring only in critical area: US – both viable and non-viable.)
- Area grading for component preparation (EU: Grade D, US Class 100,000 – Grade C equivalent in dynamic condition)
- Goggles (specific in FDA document but not in EU)
- Sterilizer load pattern record location (Validation documents in EU, batch record in US)

2. The document provides detailed guidance on many issues surrounding the process of aseptic manufacturing. Other specific associated areas that may also impact upon the sterility assurance of the product, or other issues that are directly relevant to the aseptic production of sterile products should also be referenced. Specific examples of where additional guidance should be considered, are:
   - Control of airlock and changing room environments where personnel change into aseptic area gowning, or material/equipment is introduced into the aseptic area.
   - Control of environmental air cascade within an aseptic manufacturing area using differential pressures, such that an appropriate rationale for assuring that an outward sweep of air is demonstrable.
   - Control of environments where stoppered but potentially unsealed units exit from the formally classified aseptic manufacturing area.
   - Inspection of units following the capping and sealing process.
3. The guidance includes various terminologies surrounding investigation requirements that may result in differing expectations (regarding when required and expected investigation content). It is recommended that clear descriptions of investigation requirements be included wherever "investigation" is mentioned throughout the guidance document. Alternatively, the term "investigation" could be added to the Glossary along with a clear description of expectations. The expectations for investigations should relate to the relative risk associated with the type of event. This is exemplified by the very detailed description of expected investigation approach for sterility test positives in lines 1403-1498, but is less clear in other sections of the draft guidance. Some examples of variations in terminology used in the current draft include the following:

- **Line 177**: "documented as to cause and significance"
- **Line 215**: "receive investigational attention"
- **Lines 245, 281**: "investigated"
- **Line 523**: "an investigation should be conducted promptly"
- **Lines 542-643**: "investigated in accord with Section 211.192"
- **Line 1683**: "investigated and any product that may have been impacted by the breach rejected"
- **Lines 769-771**: "comprehensive documented investigation should be conducted to determine the origin of the contamination and the scope of the problem"
- **Lines 1183-1184**: "remedial measures should be taken"
- **Line 1206**: "urges attention to the approaching action conditions"
- **Line 1207**: "more thorough investigation"

4. We recommend clarification of the scope in that the document addresses aseptic "filling" operations versus aseptic (bulk) operations in general. For added clarification, we recommend text revision to note that guidance for bulk operations is limited to Appendix 3, and that other sections of the document do not apply. With lack of specific differentiation, field investigators may opt to apply all requirements outlined for filling processes to bulk processes.
5. Closed system processing is not discussed. This processing approach is both sufficiently different from the traditional open system and widely utilized to warrant mention and integration of regulatory expectations throughout the different sections of the guidance. Alternatively, the guidance could exempt validated closed systems with validated CIP processes from its scope.
6. Specific guidance on designing/building a barrier facility should be considered through the issuance of a separate guidance document on isolators.
7. **Line Number Reference 114** - Regarding the suggested use of adjunct processing steps, if there is a clear "substantial advantage" to the patient to use a unique product image that is not tolerant to terminal sterilization, aseptic processing per the expectations of this guidance should be sufficient. The verbiage "can explore" does not provide adequate guidance or rationale to manufacturers justifying the need to develop and implement adjunct processing steps.
8. **Line Number Reference 229-280** – Consideration should be given to the fact that currently, it is not technically feasible to pre-use test hydrophobic filters for compressed gases applications.
9. **Line Number Reference 293** – On the requirement for HEPA filter leak testing in dry heat depyrogenation tunnels. This is a technical issue; filters are maintained at +300°C. The following considerations are suggested:

- Requirement should be scientifically based
- Address unfeasibility from technical standpoint
- Manufacturer recommends not to perform leak testing for safety reasons
- Safety hazard due to flash point of testing substance
- The aerosols used to produce the upstream load will remain on the filter and may cause a potential safety issue (fire) when the temperatures for dypyrogenation are applied
- Feasibility should be based on tunnel type installed

10. **Line Number Reference 331** - Regarding the location of air flow velocity tests, we recommend considering either distance from the filter face or defined distance from work surface, as it appeared in the draft concept paper. The current text suggests an expansion of the requirement with measurement at two test site locations versus one. Additionally, the location of test sites for evaluating uniform airflow velocity should be flexible and at the discretion of the individual firm provided a rationale is offered for the selected test sites.
11. **Line Number Reference 403-405** - Drains are permitted in Grade C ISO Class 8; this is harmonized with the philosophy present in the EU Annex 1 document. The use of SIP and CIP is recommended in this guideline in many areas as improving sterility assurance with regard to aseptic connections. However, it must be recognized that all of these systems require drains to remove CIP washes and or steam condensate from the systems. We recommend that instead of this statement the guidance express concern as to a potential source of contamination from a 'drain' and stress that appropriate engineering and procedural controls should be in place to prevent this from becoming a potential microbiological contamination source. We also recommend that 'open floor drains' replace 'drains'.
12. **Line Number Reference 446** – On personnel not directly in contact with sterile materials or surfaces. Some direct contact with equipment may be necessary for assembling equipment in aseptic filling suites or barriers. We suggest that again the language state that direct contact with sterile products, containers, closures or critical surfaces should be minimized. However, it is recognized that equipment assembly may necessitate such contact. Procedures should be developed to minimize contact, and post assembly disinfection should be considered.
13. **Line Number Reference 535-537** - The guidance should consider not requiring all components to be routinely characterized for microbial bioburden and pyroburden. The establishment of washing cycles capable of routinely removing > or = 3 logs of pyrogen and overkill cycles for sterilization capable of > 6 logs of inactivation of highly resistant spores obviate the need for continuous monitoring of components and or drug products. It may be appropriate for less rugged processes to receive routine monitoring of bioburden or pyroburden. The guidance should further recognize there may be alternatives to requiring routine monitoring of all aspects of processing.

14. **Line Number Reference 676** – On processing time limits. The current verbiage in the guidance suggests data are required to establish all processing times. A more effective scientific approach should be recommended, such as conducting a risk based evaluation of all processing unit operations. The assessment and the types of processes used e.g. overkill sterilization, should then be used to determine which process hold steps may require the use of data collection in order to set time limits.
15. **Line Number Reference 739** – On operator fatigue. We recommend the deletion of this reference. This is neither a measurable quantity nor a condition that should be challenged specifically during media challenges. Assuming the challenges represent the extremes of normal operating conditions, fatigue will be captured indirectly and should not be a specific media challenge criterion.
16. **Line Number Reference 1668** – Regarding uniform distribution of decontamination agent in an isolator. Technology and proper guidance on decontaminating agent concentration measurement are not adequate at this time. Evaluating distribution of agent does not require setting specifications to measure against or traceability to routine production. The addition of this requirement does not add value or assist to ensure the robustness of the validated cycles developed or used in routine production.
17. **Line Number Reference 1851-1854** – On bulk vessel integrity and transportation of bulk tanks being simulated as part of the media fill. We agree that the integrity of the process vessels used to store sterile materials should be verified and that transport and disinfection of materials into the aseptic area should be simulated during media fills. However, we do not agree that the hold times must be simulated in the fill or that the transport of the vessels themselves is necessary. There are several reasons for our comments. Vessels may be utilized for long term storage of sterile bulks and holding of media in the tanks may cause them to fail growth promotion testing. Also, there are other engineering controls or methods which may be utilized to assess the container closure integrity of the vessels utilized for holding sterile materials.

Clarifications

1. The standardized use of relevant terms throughout the guidance could reduce potential confusion. Efforts have been taken to define terms in a glossary at the end of the document, but the use of these terms in the text do not always match their intended meaning. In other cases, a specific definition has not been provided in the glossary for a term apparently being used as a synonym. Terms that are sometimes used interchangeably include: processing room and processing area, processing zones and critical area, processing line and clean area, processing line and critical area, clean area and critical area, processing area and critical room, qualification and certification, limits or specifications and levels, controlled and classified. Detailed suggestions of edits to clarify wording follow below.

2. The guidance should state that it applies to parenteral products rather than orally administered products. The latter may be prepared "aseptically" for product integrity (stability) reasons rather than for safety/patient protection reasons.
3. **Line Number Reference: 196-198**

   Original Text: "*Air in critical areas should be supplied at the point of use as HEPA-filtered laminar flow air at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations.*"

   Clarified Text: "Air in critical areas should be supplied at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations."

   Comment: The word 'laminar' has been removed as a reliance on the term "unidirectional" is sufficient.
4. **Line Number Reference**: **202-203**

   Original Text: *"Proper design and control should prevent turbulence or stagnant air in the aseptic processing line or clean area."*

   Clarified Text: "Proper design and control should prevent turbulence or stagnant air in the critical area."

   Comment: In line 159 critical area is used and defined. Although design should seek to minimize turbulence or stagnant air in the aseptic processing line or clean area it may not be possible to totally eliminate these situations. The guidance document could also reword the sentence to suggest minimizing turbulence or stagnant air in the aseptic zone.
5. **Line Number Reference:** 243

   Original Text: *"Pressure differentials between cleanrooms should be monitored continuously"*

   Clarified Text: "Pressure differentials between cleanrooms should be monitored at an appropriate frequency which establishes and demonstrates ongoing control."
6. **Line Number Reference:** 244

   Original Text: *"Deviations from established limits should be investigated"*

   Clarified Text: "Deviations from established action levels should be investigated"

   Comment: Clarify requirement for consistent interpretation.
7. **Line Number Reference:** 273

   Original Text: *"Sterilized holding tanks and any contained liquids should be held under continuous overpressure to prevent microbial contamination."*

   Clarified Text: **"***Sterilized holding tanks and any contained liquids should be held under continuous overpressure to prevent microbial contamination unless there are suitable container closure integrity data available for the subject container."*

8. **Line Number Reference:** 279-281
   Original Text: *"Filters also should be integrity tested upon installation and periodically thereafter (e.g., including at end of use)."*
   Clarified Text: "Filters that serve as sterile boundaries or supply sterile gases in direct contact with product and/or product contact surfaces also should be integrity tested upon installation and periodically thereafter (e.g., including at end of use)."
   Comment: It is critical to distinguish between gases that have a potential direct impact on product and must be sterile and those that do not need to be sterile but are used in classified areas, such as vessel jacket services or air actuation services. A risk management process is recommended to be useful in justification.
9. **Line Number Reference:** 370-375
   Original Text: "*Transfer of products should be performed under appropriate cleanroom conditions. For example, lyophilization processes include transfer of aseptically filled product in partially sealed containers. To prevent contamination, partially closed sterile product should be transferred only in critical areas. Facility design should ensure that the area between a filling line and the lyophilizer and the transport and loading procedures provide Class 100 (ISO 5) protection."*
   Clarified Text: "Transfer of products should be performed under appropriate cleanroom conditions. For example, lyophilization processes include transfer of aseptically filled product in partially sealed containers. To prevent contamination, partially closed sterile product should be transferred only in critical areas. Facility design should ensure that the area between a filling line and the lyophilizer and the open transport and loading procedures provide Class 100 (ISO 5) protection."
   Comment: The use of Annex 1 verbiage should be favored. Alternatively, the text above is recommended.
10. **Line Number Reference:** 378-379
    Original Text: **"***Carefully designed curtains, rigid plastic shields, or other barriers should be used in appropriate locations to achieve significant segregation of the aseptic processing line."*
    Clarified Text: "Carefully designed curtains, rigid plastic shields, or other barriers may be used in appropriate locations to achieve significant protection of the aseptic processing line."
11. **Line Number Reference:** 410-411
    Original Text: *"Equipment should not obstruct airflow and, in critical areas, its design should not perturb airflow."*
    Clarified Text: "Equipment should be designed to minimize disturbances to the airflow patterns."
    Comment: It is sometimes not physically possible for certain pieces of equipment not to disturb airflow patterns (stopper hoppers, for instance; filling wheels will block airflow to the vials below them).

12. **Line Number Reference:** 490
    Original Text: *"Gowning qualification should include microbiological surface sampling of several locations on a gown (e.g. glove fingers, facemask, forearm, chest, other sites)."*
    Clarified Text: "Gowning qualification should include microbiological surface sampling of several locations on a gown. Adequate rationale to justify gown test locations should be developed."
    Comment: Each firm should be able to justify the rationale for gown test locations in gown qualification. Therefore, we recommend removing the examples in the original text.
13. **Line Number Reference:** 564
    Original Text: *Each lot of components must be tested for endotoxin. "There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins. Any components failing to meet defined endotoxin limits should be rejected."*
    Clarified Text: "There should be written procedures for control of the endotoxin load of all components."
    Comment: The recommended modifications allow for depyrogenation procedures rather than acceptance criteria on incoming materials. Components are not routinely tested for endotoxin after undergoing a validated endotoxin reduction procedure (vials, stoppers, etc. are depyrogenated in conjunction with the sterilization process).
14. **Line Number Reference:** 623-625
    Original Text: *"The finished dosage form manufacturer is responsible for the review and approval of the contractor's validation protocol and final validation report."*
    Clarified Text: "The finished dosage form manufacturer is responsible for the contractor's validation protocol and final validation report."
    Comment: Remove 'review and approval'. This is covered by contractual agreement and routine audit between firms and their contractors.
15. **Line Number Reference:** 629
    Original Text: *"Container closure systems that permit penetration of air are unsuitable."*
    Clarified Text: *"Container closure systems that permit penetration of non-sterile air are unsuitable."*
16. **Line Number Reference:** 630
    Original Text: *"Any damaged or defective units should be detected, and removed, during inspection of the final sealed product. Safeguards should be implemented to strictly preclude shipment of product that may lack container closure integrity and lead to non-sterility."*

Clarified Text: "Damaged or defective units should be detected, and removed, during inspection of the final sealed product. Safeguards should be implemented to strictly preclude shipment of product that may lack container closure integrity and lead to non-sterility."
Comment: A 100% detection/removal process may not be achievable.

17. **Line Number Reference:** 660-661
Original Text: *"Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration."*
Clarified Text: "Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration, if there is no validated endotoxin reduction step."
18. **Line Number Reference:** 666
Original Text: *"Equipment should be dried following cleaning."*
Clarified Text: "Equipment should be designed to ensure proper drainage and avoid pooling of non-sterile moisture. In some cases, it may be desirable to include a drying or dynamic drainage step following cleaning, where sterilization does not proceed immediately following cleaning."
19. **Line Number Reference:** 727-728
Original Text: *"Number and type of normal interventions, atypical interventions, unexpected events (e.g., maintenance), stoppages, equipment adjustments or transfers."*
Clarified Text: "Number and type of normal interventions, and non-routine interventions and events (e.g., maintenance), stoppages, equipment adjustments or transfers."
20. **Line Number Reference:** 758
Original text: *"All personnel who enter the aseptic processing area ... should participate in medial fill"*
Clarified text: "All personnel who enter critical areas during routine operations/processing and who routinely perform aseptic manipulations must be in media fill"
21. **Line Number Reference:** 1024
Original Text: *"A production filter's integrity test specification should be consistent with data generated during filtration efficacy studies."*
Clarified Text: "Product-specific or filter integrity test medium-specific filter integrity test specifications must be established and be traceable to filtration efficacy studies."
Comment: If the filter is flushed with water after processing to get the filter back to a water baseline before executing the post-use integrity test, the flush should be validated but the integrity test specification should be based on water, the filter integrity test medium, not product. In addition, the integrity test results during the microbial retention are based on product loaded with microorganisms, not just product. The integrity test specification should not be consistent with these results

but preferably based on a statistically significant number of integrity test results using the integrity test method intended for routine use in the actual integrity test medium intended for routine use.

22. **Line Number Reference:** 1114-1115
    Original Text: *"Temperature monitoring devices for heat sterilization should be calibrated at suitable intervals, as well as before and after validation runs."*
    Clarified Text: "Temperature monitoring devices for heat sterilization should be calibrated at suitable intervals."
    Comment: The validation test equipment must be maintained in a calibrated state and undergo re-calibration at an appropriate frequency. This should be sufficient and is consistent with the expectations for manufacturing and laboratory systems used to produce and test product. Therefore, adding additional checks before and after every validation run is redundant and unnecessary. There may be cases where this is preferable to confirm the validity of the calibration status of the validation test equipment real-time with each study but this should not be a regulatory expectation.
23. **Line Number Reference:** 1284
    Original Text: *"Environmental isolates often correlate with contaminants found in a media fill or product sterility failure, and the overall environment provides valuable information for an investigation."*
    Clarified Text: "Environmental isolates may correlate with contaminants found in a media fill or product sterility failure, and the overall environment provides valuable information for an investigation."
    Comment: Environmental isolates do not often correlate with media failures and sterility failures. As a result, the utility of environmental monitoring in this sentence is overstated.

Other Comments

Line Number Reference: 143

Comment: The table is harmonized with EU requirements. A table for surface and personnel monitoring may be necessary. The specification expectation should be the same as in column 3 header.

Line Number Reference: 172

Comment: Recommend deleting "immediate" as being potentially confusing since the proximity is further defined in line 175 as "not more than one foot".

Line Number Reference: 180

Comment: 'Aseptic processing zones' should be replaced by 'critical area'.

Line Number Reference: 192

Comment: Change "certification" to "qualification" for consistency with other sections of the document.

Line Number Reference: 200

Comment: Change "within a defined space" to "within the critical area" in order to clarify the intent.

Line Number Reference: 227

Comment: 'Aseptic processing line' should be replaced by 'critical area'.

Line Number Reference: 227

Comment: This line does not constitute a clear description of activities that should be performed in Class 100,000 environments. Recommend changing to "clean equipment and product preparation steps immediately preceding final sterilization", removing the use of 'such as' as an example-giving mechanism.

Line Number Reference: 239-245

Comment: 12.5Pa is agreed as a differential between classified and unclassified areas. Additive pressures could otherwise be unfeasible to maintain. Justification of pressure cascade in use could be allowable.

Line Number Reference: 252

Comment: Although we agree that this is a desirable state, it will not always be possible to have a system that allows detection and modifications to be effected prior to reaching the action level for such parameters as pressurization, etc. We suggest that this be reworded to reflect the desirable situation, but acknowledge that this may not be possible.

Line Number Reference: 254

Comment: Replace 'pressure differential specifications with 'pressure differential action levels'.

Line Number Reference: 277

Comment: This section should be clarified to indicate that filters should be dry during their intended use. Many of the current bubble point testing methods require filters to be wetted with either alcohol or water. In cases where filters are used multiple times, such as in lyophilization cabinets, they are wetted for testing, and then blown down to dry prior to use.

Line Number Reference: 313
Comment: We recommend using the IEST standard of 10ug/L to 90 ug/L of aerosol for testing per IEST-RP-CC034.1.

Line Number Reference: 332
Comment: 'Clean area' should be replaced by 'critical area'.

Line Number Reference: 348
Comment: 'Clean area' should be replaced by 'critical area'.

Line Number Reference: 353-359
Comment: Consideration should be given to a simplified "Flow of personnel and materials should be minimized when processing is underway within the Class 100/10,000 (Grade A/B) area."

Line Number Reference: 387
Comment: We suggest changing 'Uncontrolled area' to 'Unclassified area'.

Line Number Reference: 390
Comment: We suggest changing 'Controlled' to 'Classified'.

Line Number Reference: 456
Comment: Some occlusion may be necessary for assembling equipment in aseptic filling suites or barriers. We suggest that again the language state that bodily intrusion should be minimized. Procedures should be developed to minimize such intrusion and post assembly disinfection should be considered.

Line Number Reference: 460 and 468
Comment: We recommend changing 'aseptic processing zone' to 'critical area'.

Line Number Reference: 476
Comment: We recommend changing 'aseptic processing area' to 'critical room'.

Line Number Reference: 615
Comment: Correct reference XI.C.

Line Number Reference: 709
Comment: Change to 'growth nutrient medium or non-inhibitory placebo in place of product'.

Line Number Reference: 713
Comment: Change to 'The sealed containers filled with the media are then incubated to detect microbial contamination or the placebo is tested for lack of contamination'.

Line Number Reference: 822-829
Comment: Requirement for bracketing vs. worst case is not clear. We suggest adding a line before 'For example, "If a worst-case condition can be determined for an individual processing line, the worst-case condition may be simulated for all media fills."

Line Number Reference: 854
Comment: Change to '...type of growth medium or placebo to contact...'

Line Number Reference: 952-958
Text: *"A firm's use of media fill acceptance criteria allowing infrequent contamination does not mean that a distributed lot of drug product purporting to be sterile may contain a non-sterile unit. The purpose of an aseptic process is to prevent any contamination. A manufacturer is fully liable for the shipment of any non-sterile unit, an act that is prohibited under the FD&C Act (§ 301(a) 21 U.S.C. 331(a)). FDA also recognizes that there might be some scientific and technical limitations on how precisely and accurately validation can characterize a system of controls intended to exclude contamination."*
Comment: Consider deleting this paragraph. While correct, it is not clear what value it adds to a technical guidance document since it is a legal statement.

Line Number Reference: 1020
Comment: The statement in this line represents an operations risk of contamination when filters are tested prior to use. We suggest emphasizing post-use integrity testing.

Line Number Reference: 1033
Comment: Modify to 'Those surfaces that are in the vicinity of sterile product or container closures, but do not directly contact the product should also be rendered sterile where possible and where reasonable contamination potential exists.' Stationary machine surfaces in the vicinity of sterile product are unlikely to be able to be sterilized.

Line Number Reference: 1158
Comment: Given that all specifications are now in cubic meters, and cubic meter sample volumes will be collected, field investigators are unlikely to accept less. However, the use of the ISO-14644-2 formula (and former FS 209E) for minimum sample volumes should be offered as an option to Industry.

Line Number Reference: 1163
Comment: Replace 'aseptic processing clean area' with 'critical area'.

Line Number Reference: 1229
Comment: The text in this line may imply that a batch sterilization process may be required versus the mixing of sterile components (i.e., sterile concentrated disinfectant and sterile WFI). Language similar to Annex 1, paragraph 38, should be considered. We suggest adding 'Disinfectants should be rendered sterile and used for a limited time, unless there is sufficient justification to do otherwise.' or modifying to 'Disinfectants should be prepared from sterile precursors using water of at least WFI quality, or should be rendered sterile prior to use.' The reason for using sterile disinfectants is to prevent introducing resistant organisms into the aseptic processing areas. WFI is extremely low bioburden, and does not provide a significant risk of contaminating the area – and the solution does not remain sterile during use.

Line Number Reference: 1330
Comment: The text in this line appears inconsistent with text on single, isolated action levels (1182-1184) with respect to what needs to be done when action level results are obtained.

Line Number Reference: 1363
Text: '*Study documentation should include evaluation of whether microbial recovery from inoculated controls and product samples is comparable throughout the incubation period.*'
Comment: This is more restrictive than the requirements in EP or USP. It suggests that if the growth is seen slower, e.g. day 4 vs. day 3 for the control, then the test is not satisfactory and must be modified. We think that the USP procedure is adequate to demonstrate the sterility test validation. We do not agree that demonstration of equivalence throughout the incubation period is scientifically justified. We do agree the key is to assure that the test would not produce false negative results.

Line Number Reference: 1406
Comment: Quote in footnote 12 is different for clean room testing vs. isolator. See definition USP 71, p. 1883.

Line Number Reference: 1423
Comment: Even with the most modern techniques and databases, it is not always possible to identify all isolates to species level.

Line Number Reference: 1445
Comment: Keeping separate trends seems necessary only in the case of processes where sterility assurance is out of control. The trending stated should be event driven and used as an investigational tool; it should not be required on a routine/ongoing basis.

Line Number Reference: 1597
Comment: Consider changing to European Annex 1 specifications, which brings consistency with the rest of the document.

Line Number Reference: 1637
Comment: Standardize on terms used: 'mousehole', 'exit port', and 'process egress points' are all used in previous paragraphs of this section.

Line Number Reference: 1688-1689
Comment: The use of the words, 'liquid stream' neglects powders. Terms such as, 'product contact surfaces' should be used instead. Therefore, edit the sentence as follows, 'To ensure sterility of product contact surfaces from the start of each operation, the entire path of product contact surfaces should be sterilized.'

Line Number Reference: 1810-1870
Comment: Please clarify in the text that this section only applies to formulation prior to filling and not to upstream bulk processes.

Line Number Reference: 1855-1856
Comment: We assume that this requirement applies to 'formulation' just prior to filling and is not applicable to upstream processes. Process simulations for upstream processes should be performed once per year based upon an evaluation of risk of the process. Please clarify in the text.

Line Number Reference: 1985
Comment: The decontamination definition should not be limited to sporicidal agent methods. Text following the word 'bioburden' should be removed.

We welcome the opportunity to provide feedback on the *Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing.*

Sincerely,

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