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VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

PhRMA

November 4, 2003

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

Re: Draft Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice [Docket No. 2003D–0382, 68 *Federal Register*, 52782-52783, September 5, 2003]

Dear Sir/Madam:

The following comments on the above noted draft guidance document regarding "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice" are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA).

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer and more productive lives. Investing more than $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

The following general observations highlight major areas where the usefulness of the guidance may be enhanced.

1. **Several recommendations seem unnecessarily specific and may prevent future innovations as technological advances become available.**
   Specific recommendations on performing HEPA filter testing, facility design for a lyophilizing operation, and statements regarding the use of isolators are examples.
   a. For HEPA filter testing, the guidance should allow the flexibility to use more modern and improved techniques such as laser counters (line 312).

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b. Facility design for lyopholization processes (line 373) should allow for the use of isolator technology or laminar flow transfer carts.
c. The guidance acknowledges the advantages that an appropriately designed and maintained isolator can provide over classical aseptic processing. However the stricter controls for isolators compared to what is required for traditional manned conditions could discourage their use. The discussion on isolator leaks is an example. Isolators are designed to have a higher pressure then surrounding areas, which is an analogous design approach as used with traditional clean rooms. Isolator component leaks do not necessarily constitute a "significant breach" due to this positive pressure.

2. **This guidance should be harmonized with the European GMP requirements.**
The creation of a unified global aseptic standard is both feasible and necessary. In particular, Table 1 deviates from the European GMP requirements.

3. **Clean rooms should be classified under static or as-built conditions.**
Classification under these conditions is defined in ISO 14644. Evaluation under dynamic conditions should be part of the environmental monitoring program.

4. **The sterility testing section should be removed.**
Details on sterility testing are appropriately covered in the USP. Additional discussion in this guidance increases the risk of inconsistent requirements.

5. **There is inconsistent guidance within the current draft regarding process simulations.**
The guidance states that media fills should closely simulate the same exposure that the product itself will undergo. Other sections emphasize the use of worst-case conditions. Stacking all potential worst-case situations into each media run does not represent an appropriate challenge simulating normal processing. Additionally the guidance requires the inclusion of media-filled units that normally would be removed as per SOP (e.g. defined line clearance), which is not representative of the drug manufacturing process. Regarding the line speed during simulations, one sentence says that the *range* of speeds should be addressed, while another specifies *worst case*.

Inconsistent guidance is given for the duration of runs. The guidance states that the *duration* of aseptic processing operations is a major consideration in determining the *size* of the media fill. It also specifies media fill *sizes* that are not representative of *production duration*. The

duration of media fill runs should be dictated by the time needed to simulate operations and interventions, and prepare the defined number of units.

We appreciate the opportunity to comment on the draft guidance on aseptic processing cGMPs. We trust that you will give careful consideration to our attached comments as you finalize the guidance.

Please contact me if you have any questions.

Sincerely,

Alice E. Till

Alice E. Till, Ph.D.

CC P. Cooney, J. Famulare, R. Friedman, D. Horowitz, H. Winkle

Attachment

SCORECARD: PhRMA Comments on:
Draft FDA Guidance "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice"
[Docket No. 2003D–0382]
September 2003

Total Number of Changes Suggested: 118

Section	Guidance Line	Comment	Rationale
General		There are some aspects of this draft guidance document that appear to improve global harmonization, for example, approach to aseptic processing vs. Terminal Sterilization and approach to environmental monitoring at rest & in operation (dynamic condition). However, 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 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) • Introduction of a class 1000 area • 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) • Averaging of microbiological results • Sterilizer load pattern record location (Validation documents in EU, batch record in US)	

Section	Guidance Line	Comment	Rationale
General		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"	
General		We recommend clarification in the scope, 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.	
General		Closed system processing is not discussed. This processing approach though, 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.	

Section	Guidance Line	Comment	Rationale
General		Specific guidance on designing/building a barrier facility should be considered through the issuance of a separate guidance document on isolators.	
General		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 been 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.	
General		21 CFR Regulation Citations: Throughout the draft guidance document, 21 CFR Part 210 and 211 regulations are cited. We suggest that guidance be provided to support each regulation cited.	The non-descript nature of the regulation results in different interpretations during Pre-approval inspections and GMP investigations.
II.B Technical Framework	70-71	Current Text: "There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization." Comment: This sentence should be changed to exclude terminally sterilized products from this guidance. Proposed Revision: "There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization, and as such this guidance does not apply to terminally sterilized products."	As the guidance states there are basic differences between the production of terminally sterilized products sterile drug products using aseptic processing and production using terminal sterilization and it should be clear that this guidance does not apply to terminally sterilized products.
III. Scope	114-115	Current Text: "In such cases, a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility confidence." Comment: The sentence is a statement without guidance as to when such evaluation is required. Proposed Revision: Delete sentence.	The scope of this document is to discuss current GMP issues and as such it is inappropriate to discuss product development and the review process.

Section	Guidance Line	Comment	Rationale
IV. Buildings and Facilities	131-132	Current Text: "Critical areas and support areas of the aseptic processing operation should be classified and supported by microbiological and particle data obtained during qualification studies." Comment: For clarity, we suggest adding text and providing particulate/microbial levels to define *"critical areas"* and *"support areas"*.	Statement is unclear.
IV. Buildings and Facilities	136	Current Text: "The aseptic processing facility monitoring program should also assess conformance with specified clean area classifications under dynamic conditions on a routine basis." Proposed Revision: "The aseptic processing facility's routine environmental monitoring program should assess the environment under dynamic conditions."	It is unclear whether the statement applies to routine environmental monitoring.
IV. Buildings and Facilities Table 1	142	Current Text: "TABLE 1- Air Classifications[a]" Proposed Revision: "TABLE 1 - Air Monitoring for Aseptic Processing"	Since the table covers more than just air classification requirements (i.e., microbial levels) and pertains solely to aseptic processing areas, we suggest revising the title of the table.
IV. Buildings and Facilities Table 1	142-144	Current Text: "Clean Area Classification (0.5 μm particles/ft3)". Proposed Revision: "Clean Area Classification (≥0.5 μm particles/ft3)".	We recommend the value should be presented in the table header of Column 1 as the *maximum* number of particles.
IV. Buildings and Facilities Table 1	147-148	Current Text: Footnote (b) – "ISO 1644-1 designations provide platform particle concentration values for clean rooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A." Comment: We suggest that there should also be international harmonization in microbiological action levels. The proposed microbiological limits are stricter than both the current USP and the EU guide Annex. The EU guide permits averaging, which is not mentioned in the FDA guidance and so presumably not permitted.	

Section	Guidance Line	Comment	Rationale
IV. Buildings and Facilities Table 1	152	Current Text: Footnote (e) – "Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants." Comment: It is unclear why Table 1 includes the value of "1" if Class 100 (ISO 5) environments should "normally yield no microbiological contaminants". Footnote (e) adds confusion as to whether the action level is 1 or zero. We suggest adding a note that averaging would be consistent with EU GMP. Proposed Revision: We suggest that this footnote either be deleted, or replaced with the following text: "The count should be <1, as verified by averaging."	
IV.A Critical Area - Class 100 (ISO 5)	159-160	Current Text: "A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions designed to preserve sterility." Proposed Text: "A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions designed to preserve sterility. Some special operations, such as transport of containers from the filling line to a lyophilizer may occur via alternate validated approaches, such as an over-pressurized sealed transfer carts."	The current text does not allow for the use of sealed carts to transport products from the filling line to the lyophilizer without the use of elaborate transport carts.
IV.A Critical Area - Class 100 (ISO 5)	174 304 310 Footnote 7 969 976 2001 2049	Current Text: "micron" Proposed Text: Replace "micron" with "micro meter"	Harmonization

Section	Guidance Line	Comment	Rationale
IV.A Critical Area - Class 100 (ISO 5)	182-183	Current Text: "Regular monitoring should be performed during each shift". Comment: Qualify "regular". Proposed Revision: "Regular monitoring should be performed at least once during each shift or as appropriate."	
IV.A Critical Area - Class 100 (ISO 5)	183	"Shift" needs defining precisely. It has no real meaning except as a team of people. Here it is a time function apparently. If a Team (Shift) works for 2.5 hours and takes a break, works 2.5 hours and takes a second break, works 2.5 hours again and takes a third break, is this considered one, two or three shifts?	
IV.A Critical Area - Class 100 (ISO 5)	196-198	Current 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." Proposed Revision: "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."	The word 'laminar' has been replaced with unidirectional' with this exception.

Section	Guidance Line	Comment	Rationale
IV.A Critical Area - Class 100 (ISO 5)	198-200 Footnote 4	Current Text: "The velocity parameters established for each processing line should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within a defined space (Ref.3).[4]" and Footnote 4: "A velocity from 0.45 to 0.51 meters/second (90 to 100 feet per minute) is generally established, with a range of plus or minus 20 percent around the set point. Higher velocities may be appropriate in operations generating high levels of particulates." Comment: For clarity, we suggest adding text to define "defined space". With regard to Footnote 4, it is suggested that it is clearly stated that this is a guidance value, which then would be harmonized with the EU GMPs, Annex 1. Where it is scientifically and technically justified & validated, we suggest that the option should be open to use any alternative velocity that is effective, not simply a "higher" one. Depending on the exact facilities & process, it may prove better to use a lower, controlled, velocity. Where this is validated, the approach should not be unnecessarily proscribed. For example, if smoke studies at lower velocities show better laminarity, then it should be acceptable to operate in this defined range.	
IV.A	202-203	Current Text: "Proper design and control should prevent turbulence or stagnant air in the aseptic processing line or clean area." Proposed Revision: "Proper design and control should prevent turbulence or stagnant air in the critical area."	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.

Section	Guidance Line	Comment	Rationale
IV.A Critical Area - Class 100 (ISO 5)	214	Current Text: "Air monitoring of critical areas should normally yield no microbiological contaminants" Comment: The current text is inconsistent with Table 1 that sets the action level at 1 cfu. Proposed Revision: "A target of no microbiological contaminants for air monitoring samples from Class 100 (ISO 5) environments should be the goal. All excursions should receive investigation attention and occasional microbial counts may be acceptable with proper investigation."	
IV.B Supporting Clean Areas	226-227	Current Text: "An area classified at Class 100,000 (ISO 8) would be used for less critical activities (such as initial equipment preparation)." Proposed Text: "An area classified at Class 100,000 (ISO 8) would be used for less critical activities (such as initial equipment and component preparation)."	Expand examples of less critical activities.
IV.B Supporting Clean Areas	229-230	Current Text: "Depending on the operation, manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5)." Proposed Revision: Delete sentence.	We suggest that the additional category ISO 6 (Class 1000) in the context of Pharmaceutical manufacturing should be deleted for the following reasons: • There is no real technical need for this class. • The category does not exist in any other pharmaceutical references. • Strides should be made toward international harmonization whereas the introduction of a new class tends to move against this. • The microbiological criteria for this category are new and are not consistent with any other existing document on this topic, including the USP. • The proposed new category would generate uncertainty as to what criteria would be expected, depending on the process (ref. Line 229 "depending on the operation")

Section	Guidance Line	Comment	Rationale
IV.C Clean Area Separation	238-241	Current Text: "For example, a positive pressure differential of at least 12.5 Pascals (Pa)[1] should be maintained at the interface between classified and unclassified areas. This same overpressure should be maintained between the aseptic processing room and adjacent rooms (with doors closed)." Proposed Revision: "Overpressure should be maintained between the aseptic processing room and adjacent rooms of different classification (with doors closed)."	• Unnecessary specificity. It should not be necessary to maintain any specific value, as long as a correct cascade is maintained (as discussed in line 241). • The draft guidance indicates that differentials of 12.5 Pascals need to be maintained with respect to all rooms adjacent to an aseptic processing room. If this includes rooms of the same classification, then this is in excess of existing GMP requirements, which require this differential only between rooms of different classification. • Due to the cumulative differential pressure steps, this may result in very high pressure (relative to ambient) at the central core. It may also cause problems with balancing the overall cascades of airflow / pressure differentials (e.g., where a hot air sterilizer tunnels is installed there would be a very high differential between outlet and inlet to the tunnel).
IV.C Clean Area Separation	243-245	Current Text: "Pressure differentials between cleanrooms should be monitored continuously throughout each shift and frequently recorded, and deviations from established limits should be investigated." Proposed Revision: "Pressure differentials between cleanrooms should be monitored continuously throughout and recorded at the beginning and end of each shift. All alarms should be recorded, and deviations from established limits should be investigated."	The requirement to frequently record values from a validated system that is within specification is overly burdensome and should be changed.
IV.C Clean Area Separation	247-249	Current Text: "For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour would be typically acceptable." Proposed Revision: "For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve and maintain the desired classification is required. Twenty or more air changes per hour may be needed, depending on the design and use of the room."	The number of air changes required depends on multiple factors. Air changes substantially higher than 20 per hour are normally unnecessary and may be difficult to achieve depending on the size & design of the area.

Section	Guidance Line	Comment	Rationale
IV.D.1 Membrane	264-266	Current Text: "Compressed gases such as air, nitrogen, and carbon dioxide are often used in cleanrooms and are frequently employed in operations involving purging or overlaying." Proposed Revision: "Compressed gases such as air, nitrogen, and carbon dioxide are often used in cleanrooms and are frequently employed in operations involving purging and/or overlaying."	Statement is unclear.
IV.D.1 Membrane	272-273	Current Text: "Sterilized holding tanks and any contained liquids should be held under continuous overpressure to prevent microbial contamination." Proposed Revision: "Sterilized holding tanks and any contained liquids should be held under continuous overpressure to prevent microbial contamination. Alternative techniques such as pressure/vacuum testing of the vessel/system, use of continuous overpressure, or properly validated non-pressurized systems may be appropriate."	• Emphasis should be put on confirmation of integrity rather than an absolute requirement to have overpressure in all cases. Overpressure on a holding vessel may adversely affect the filling process, for example, dosing consistency. Hence, it is often technically difficult to meet the requirement to have the holding vessels always subjected to overpressure during the filling process. Positive pressure maintenance is a good technique, but is not currently mandated by GMPs, provided that the vessel integrity and filter integrity are controlled. • Sterility can be maintained with other procedures, such as sterile vent filters. • Manufacturing situations where receiving carboys are employed or tanks that are properly sealed may not be amenable to constant overpressure. This should not be expected where practitioners have properly validated sterile holding systems via media fills.
IV.D.1 Membrane	280	Current Text: "Filters also should be integrity tested upon installation and periodically thereafter (e.g., including at end of use)." Proposed Revision: "Filters also should be integrity tested upon installation and at least once per year thereafter (e.g., including at end of use)."	Vague requirement.

Section	Guidance Line	Comment	Rationale
IV.D.2 High-Efficiency Particulate Air (HEPA)	287-289	Current Text: "Thereafter, leak tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room." Comment: We suggest that the minimum frequencies for testing should be based on ISO recommendations (ISO 14644-2). More frequent testing may be done based on risk analysis and routine performance data. We also suggest that testing be performed twice per year in the critical zone (ISO 5) and once per year for HEPA filters in lower categories.	
IV.D.2 High-Efficiency Particulate Air (HEPA)	292-294	Current Text: "Among the filters that should be leak tested are those installed in dry heat depyrogenation tunnels commonly used to depyrogenate glass vials."	• Testing HEPAs in dry heat ovens/tunnels is dangerous due the volatility, combustibility, and potential toxicity/carcinogenicity of challenge materials when heated. • We suggest adding text to provide clarification that leak tests on HEPA filters located in the heating zone of dry heat depyrogenation tunnels need to be conducted at the room-temperature state. • Feasibility should be based on tunnel type installed.
IV.D.2 High-Efficiency Particulate Air (HEPA)	297-298	Current Text: "Dioctylphthalate (DOP) and Poly-alpha-olefin (PAO) are examples of appropriate leak testing aerosols." Proposed Revision: "Di-Ethyl-Hexyl-Phthalate (DEHS) and Poly-alpha-olefin (PAO) are examples of appropriate leak testing aerosols."	• Concerns that DOP is a carcinogen have been raised; it should not be proposed for use. • Other leak testing agents are also appropriate. We suggest that Di-Ethyl-Hexyl-Phthalate (DEHS) be added to the list of appropriate leak testing aerosols, as this is a well-defined compound with specific characteristics. We also suggest that a reference to the international standard EN1822 be added to the guidance as it contains a list of proven and recommended aerosol materials.

Section	Guidance Line	Comment	Rationale
IV.D.2 High-Efficiency Particulate Air (HEPA)	310-316	Current Text: "Performing a leak test without introducing a sufficient upstream challenge of particles of known size upstream of the filter is ineffective for detecting leaks. For example, depending on the accuracy of the photometer, a DOP challenge should introduce the aerosol upstream of the filter in a concentration ranging from approximately 25 to 100 micrograms/liter of air at the filter's designed airflow rating. The leak test should be done in place, and the filter face scanned on the downstream side with an appropriate photometer probe, at a sampling rate of at least one cubic foot per minute." Comment: • The text is too specific regarding the challenge. The challenge should be sufficient to verify the filter's efficiency rating. • See previous comments regarding DOP (line 296). • We suggest that this section be revised to allow for the use of alternatives that provide more modern and improved techniques, such as laser counters. The draft guidance currently refers only to photometers for the detection of particles. The laser counter method is a reference method in ISO/DIS 14644-3. The final guidance document should allow for developments and new techniques. The use of laser particle counters as detection instruments is now common in the Industry.	
IV.D.2 High-Efficiency Particulate Air (HEPA)	326-328	Current Text: "This testing is usually done only on a semi-annual basis. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters)." Comment: • The intervals of regular monitoring are not specified, but there is an implication that it should be performed more regularly than once every 6 months. This may be unnecessarily frequent as airflow velocity changes only occur gradually over long periods of time. We suggest that velocity tests concurrent with the filter leak testing should be adequate. • Current text is vague with regards to defining "periodic".	

Section	Guidance Line	Comment	Rationale
IV.D.2 High-Efficiency Particulate Air (HEPA)	330-332	Current Text: "Airflow velocities are measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area". Proposed Revision: "Airflow velocities are measured 6 inches from the filter face or at a defined distance proximal to the work surface for HEPA filters in the critical area."	• Six inches is an arbitrary distance. • The location of velocity measurements should not be prescribed by FDA, only that whatever location is chosen that it be used over time so that velocity comparisons could be reasonably made. • Redundant with requirements identified in line 200 and corresponding footnote. • The current text suggests an expansion of the requirement with measurement at two test site locations versus one.
IV.E. Design	348	Current Text: "...high assurance of sterilty (Ref. 4)." Proposed Revision: "...high assurance of sterility (Ref. 4)."	Minor typographical error (sterility).
IV.E Design	370-372	Current Text: "For example, lyophilization processes include transfer of aseptically filled product in partially sealed containers." Proposed Revision: "For example, lyophilization processes include transfer of aseptically filled product in partially sealed/closed containers."	For clarity, we suggest rephrasing this sentence.
IV.E Design	373-375	Current Text: "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" Proposed Revision: "Facility design should ensure that the area between a filling line and the lyophilizer and the transport and loading procedures provide ISO 5 protection"	• The current wording could be interpreted as meaning that the room itself must be classified to ISO 5 in the area between filling and the lyophilizer. We suggest revising the text so that the guidance document simply states that the protection should be according to ISO 5. There are several other methods of achieving this; for example isolator technology or laminar flow transfer carts. • Current wording does not recognize the potential of closed containers moving through higher classified areas. A closed container can protect partially stoppered vials from adventitious contamination.

Section	Guidance Line	Comment	Rationale
IV.E Design	378-379	Current 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." Proposed Revision: "Carefully designed curtains, rigid plastic shields, or other barriers may be used in appropriate locations to achieve significant protection of the aseptic processing line."	
IV.E Design	403-405	Current Text: "With rare exceptions, drains are not considered appropriate for classified areas of the aseptic processing facility" Proposed Revision: "With rare exceptions, facility drains are not considered appropriate for Class 100 (ISO Class 5) or Class 10,000 (ISO Class 7) areas of the aseptic processing facility"	• The glossary indicates the definition of "aseptic processing facility" as including the entire building, not only the aseptic zone. • We agree that drains should not be present in the higher categories of classified areas (e.g., aseptic processing rooms). However, correctly designed drains are necessary in some of the lower category areas, for example, locations of washers and compounding. • We suggest that the position set forth in the guidance document should be more precisely defined. We also suggest harmonizing the position with the EU GMPs, requiring that sinks and drains should be prohibited in "ISO 5" to "ISO 7" areas (classified in dynamic state). Drains should be excluded from critical and direct support locations, but are required in some of the process rooms that are not directly connected to the critical aseptic operation. • 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.

Section	Guidance Line	Comment	Rationale
IV.E Design	410-411	Current Text: "Equipment should not obstruct airflow and, in critical areas, its design should not perturb airflow" Proposed Revision: "Equipment should be designed to minimize disturbances to the airflow patterns"	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).
V.A Personnel	432-433	Current Text: "Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations." Proposed Revision: "There should be adequate supervision to ensure each operator's conformance to written procedures during actual operations."	Existing procedures, including routine supervision, documented training, deviation records and internal audits are adequate to give a comprehensive control. The addition of yet more evaluation seems unnecessarily complex.
V.A Personnel	439-442	Current Text: • "Contacting sterile material only with sterile instruments Sterile instruments (e.g. forceps) should always be used in the handling of sterilized materials." Comment: Current text is impractical. Proposed Revision: "Equipment set-up activities typically present a unique set of challenges to using proper aseptic techniques. Direct contact between gloved hands and the critical surfaces of sterilized equipment parts (surface which subsequently have direct product contact) is to be avoided."	Some direct contact with equipment may be necessary for assembling equipment in aseptic filling suites or barriers. For example, assembling and fitting sterilized filling pumps is impossible with forceps. Since set up is notoriously the most hazardous part of an aseptic operation, this clause should be re-written or excluded because it is not possible to comply with in practice.

Section	Guidance Line	Comment	Rationale
V.A Personnel	442	Current Text: "Between uses, instruments should be placed only in sterilized containers". Comment: The text indicates that instruments are permitted only to be stored in sterilized containers. For clarity, we suggest adding text indicating that storage of instruments can be permitted in a protected environment where the item does not touch a non-sterilized surface. For example, instruments can be stored in an appropriate location under ISO 5 protective air. Proposed Revision: "Between uses, proper procedures should be used to maintain instrument sterility. For example, storage in an appropriate location under ISO 5 protective air."	
V.A Personnel	443	Current Text: "Instruments should be replaced as necessary throughout an operation." Proposed Revision: "Instruments should be replaced when any aspect of sterility is thought to be compromised so as to render the instrument non sterile, throughout the operation."	Current sentence unclear.
V.A Personnel	472-473	Current Text: "Prior to and throughout aseptic operations, an operator should not engage in any activity that poses an unreasonable contamination risk to the gown." Comment: Current text is too vague. Proposed Revision: "An operator should be trained to minimize contamination risk to the gown prior to and throughout aseptic operations."	

Section	Guidance Line	Comment	Rationale
V.A Personnel	489-490	Current Text: "Gowning qualification should include microbiological surface sampling of several locations on a gown (e.g. glove fingers, facemask, forearm, chest, other sites)." Proposed Revision: "Gowning qualification should include microbiological surface sampling of several locations on a gown. Adequate rationale to justify gown test locations should be developed."	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.
V.A Personnel	493-494	Current Text: "Semi-annual or yearly requalification is sufficient for automated operations where personnel involvement is minimized." Comment: Semi-annual is not current practice, and is more stringent than cGMP. Proposed Revision: "Gowning requalification may be repeated based either upon issues raised in the change control program and/or on a timed basis such as annually."	
V.B Laboratory Personnel	503-505	Current Text: "The basic principles of training, aseptic technique, and personnel qualification in aseptic manufacturing also are applicable to those performing aseptic sampling and microbiological laboratory analysis". Proposed Revision: Delete "and microbiological laboratory analysis." Add "Those performing microbiological laboratory analyses should have appropriate education, training, and experience in microbiological techniques."	

Section	Guidance Line	Comment	Rationale
V.C Monitoring Program	515-517	Current Text: "The quality control unit should establish a more comprehensive monitoring program for operators involved in operations, which are especially labor intensive (i.e., those requiring repeated or complex aseptic manipulations)." Comment: We suggest that this is an unnecessary division that effectively gives two classes of filling operators. This is very difficult to administer. Also, it is important that all staff in the area partaking in permitted interventions are adequately monitored. Having different monitoring procedures may be mistaken to indicate that some simpler operations are not critical, when in fact they are. The most negative impact on the product is created by the kind of intervention performed by the operator and not by the degree of labor intensiveness. All operators who may take part in permitted interventions that could conceivably have a potential risk of product contamination must be monitored. The microbiological limits are already very tight indeed and it is unreasonable to have different classes of "criticality".	
VI.A Components	537-540	Current Text: "It is important to characterize the microbial content of each component that could be contaminated and establish appropriate acceptance limits based on information on bioburden. Knowledge of bioburden is critical in assessing whether the sterilization process is adequate" Comment: The current text over-simplifies this issue. Proposed Revision: Add: "Only limited bioburden data for components subject to overkill sterilization or depyrogenation cycles is necessary."	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.
VI.B.1 Preparation	600	Current Text: "Pyrogen on plastic containers can be generally removed by multiple WFI rinses." Proposed Revision: "Pyrogen on plastic containers can be generally removed by adequate procedures such as multiple hot (85° C) WFI rinses."	Added clarification.

Section	Guidance Line	Comment	Rationale
VI.B.1 Preparation	608-610	Current Text: "At minimum, the initial rinses for the washing process should employ Purified Water, USP, of minimal endotoxin content, followed by final rinse(s) with WFI for parenteral products." Comment: Current text is too specific, and unnecessary. Proposed Revision: "At minimum, the initial rinses for the washing process should be sourced from at least Purified Water, USP, of minimal endotoxin content, followed by final rinse(s) with WFI for parenteral products. The use of recycled WFI from the final rinse is acceptable if validated."	Many washers use recycled final rinse water for initial rinses. This water is not tested to meet Purified Water, USP.
VI.B.1 Preparation	618-620	Current Text: "Silicone used in the preparation of rubber stopper should meet appropriate quality control criteria and not have an adverse effect on the safety, quality, or purity of the drug product." Proposed Revision: "Silicone used in the preparation of rubber stoppers should meet appropriate quality control criteria and not have an adverse effect on the safety, quality, or purity of the drug product, as determined by appropriate quality control testing."	Added clarification.
VI.B.2 Inspection of Container Closure System	629-630	Current Text: "A container closure system that permits penetration of air, or microorganisms, is unsuitable for a sterile product." Comment: This is not necessarily true of air. Proposed Revision: "A container closure system that permits penetration of microorganisms is unsuitable for a sterile product."	• Some bag containers may have very low water vapor transmission levels, which over time (years) make the product unsuitable chemically, but has no negative impact on the microbiological quality of the product. • Penetration by air occurs in many forms of packaging that is used for sterilization (e.g. sterilization packs & bags). It is the penetration of microorganisms that is the risk in these cases. Hence, we suggest that this statement is not correct in cases where the containing pack is designed to filter the air free of microbial contaminants.

Section	Guidance Line	Comment	Rationale
VII Endotoxin Control	660-661	Current Text: "Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration." Comment: We suggest that clarification be provided regarding this statement. Proposed Revision: "Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration. For example, promptly cleaning and drying equipment with validated procedures will help control endotoxin contamination."	It is unclear what is expected on this point, particularly regarding the frequency of both prior to and after sterilization. If this statement relates specifically to cleaning validation, then perhaps it is a reasonable concept. However, if it relates to routine testing, the approach seems unreasonable.
VII Endotoxin Control	664-666	Current Text: "Some clean-in-place procedures employ initial rinses with appropriate high purity water and/or a cleaning agent (e.g., acid, base, surfactant), followed by final rinses with heated WFI." Proposed Revision: "Some clean-in-place procedures employ initial rinses with appropriate purity water and/or a cleaning agent (e.g., acid, base, surfactant), followed by final rinses with heated WFI. The use of recycled WFI from the final rinse is acceptable if validated."	Many washers use recycled final rinse water for initial rinses. This water is not tested to meet Purified Water, USP.
VIII. Time Limitations	675-678	Current Text: "Time limits should be established for each phase of aseptic processing. Time limits should include, for example, the period between the start of bulk product compounding and its filtration, filtration processes, product exposure while on the processing line, and storage of sterilized equipment, containers and closures."	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.

Section	Guidance Line	Comment	Rationale
VIII. Time Limitations	682-687	Current Text: "The total time for product filtration should be limited to an established maximum to prevent microorganisms from penetrating the filter. Such a time limit should also prevent a significant increase in upstream bioburden and endotoxin load. Sterilizing-grade filters should generally be replaced following each manufactured lot. Because they can provide a substrate for microbial attachment, maximum use times for those filters used upstream for solution clarification or particle removal should also be established and justified." Proposed Revision: Add the following sentence to the end of the paragraph: "Integrity testing before and after use should also be specified in standard operating procedures that are pertinent to the use of these filters and appropriate investigations performed on any lot suspected of being compromised."	Added clarification.
IX.A.1 Study Design	722-724	Current Text: "Media fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a worst-case approach. The media fill program should address applicable issues such as:" Comment: Stacking all potential worst-case situations into each media run does not represent an appropriate challenge simulating normal processing. Proposed Revision: "Media fill studies should simulate aseptic manufacturing operations as closely as possible. Media fill studies should be designed to address applicable issues such as:"	
IX.A.1 Study Design	727	Current Text: "...number and type of normal interventions" Proposed Revision: Delete "number"	Number of typical interventions is proportional to the length of the operation. Should not specify "number".

Section	Guidance Line	Comment	Rationale
IX.A.1 Study Design	739	Current Text: "....operator fatigue" Proposed Revision: Delete "operator fatigue"	• We consider it to be generally impractical to artificially simulate fatigue, as the process should be designed to minimize fatigue. • Environmental and personnel monitoring is a better assessment of operator fatigue; this should not be required for media fill.
IX.A.2 Frequency and Number of Runs	757-758	Current Text: "For example, the evaluation of a shift should address its unique time-related and operational features" Proposed Revision: "For example, the evaluation of a shift change should address the movement of personnel in and out of the aseptic processing and change rooms including de-gowning and gowning procedures."	Clarify.
IX.A.2 Frequency and Number of Runs	758-760	Current Text: "All personnel who enter the aseptic processing area, including technicians and maintenance personnel, should participate in a medial fill at lease one a year." Comment: Planned interventions during media fills are logical and reasonable, however, requiring every person from maintenance who may enter the aseptic area to participate once a year may not be practical.	
IX.A.3 Duration of Runs	780-783	Current Text: "The duration of aseptic processing operations is a major consideration in determining the size of the media fill run. Although the most accurate simulation model would be the full batch size and duration because it most closely simulates the actual production run, other appropriate models can be justified" Proposed Revision: Delete sentences	Elsewhere in this section we specify media fill sizes that are not representative of production duration.

Section	Guidance Line	Comment	Rationale
IX.A.3 Duration of Runs	783-784	Current Text: "In any study protocol, the duration of the run and the overall study design should adequately mimic worst-case operating conditions and cover all manipulations that are performed in the actual processing operation" Comment: The current text is inconsistent. Elsewhere in the document it mentions that atypical interventions may be rotated. Proposed Revision: "In any study protocol, the duration of the run and the overall study design should adequately mimic appropriate designed worst-case process operations."	
IX.A.3 Duration of Runs	795-796	Current Text: "For lyophilization operations, unsealed containers should be exposed to pressurization and partial evacuation of the chamber in a manner that simulates the process." Comment: The current sentence is incorrect. Containers should not be exposed to 'pressurization'. Proposed Revision: "For lyophilization operations, unsealed containers should be exposed to partial evacuation of the chamber in a manner that simulates the process. For routine aerobic media fill tests, precautions should be taken that ensure that the medium remains in an aerobic state."	

Section	Guidance Line	Comment	Rationale
IX.A.5 Line Speed	822-829	Current Text: "The media fill program should adequately address the range of line speeds (e.g., by bracketing all vial sizes and fill volumes) employed during production. Each individual media fill run should evaluate a single worst-case line speed, and the speed chosen for each run during a study should be justified. For example, use of high line speed is often most appropriate in the evaluation of manufacturing processes characterized by frequent interventions or a significant degree of manual manipulation. Use of slow line speed is generally appropriate for evaluating manufacturing processes characterized by prolonged exposure of the sterile drug product and container closures in the aseptic area." Proposed Revision: "The media fill program should adequately address the range of line speeds (e.g., by bracketing all vial and fill volumes) employed during production. Each individual media fill run should evaluate a single worst-case line speed, and the speed chosen for each run during a study should be justified and documented. For example, use of high line speed is often most appropriate in the evaluation of manufacturing processes characterized by frequent interventions or a significant degree of manual manipulation. Use of slow line speed is generally appropriate for evaluating conventional manufacturing processes allowing prolonged exposures of the sterile drug product and container closures in the aseptic area."	One sentence says that the range of speeds should be addressed, while the other specifies "worst case".
IX.A.6 Environmental Considerations	837-839	Current Text: "To the extent standard operating procedures permit stressful conditions, it is important that media fills include analogous challenges to support the validity of these studies" Comment: The current text is unnecessary and overly strict. Proposed Revision: Delete sentence	The statement is unclear as to expectations and does not represent realistic conditions for simulation.

Section	Guidance Line	Comment	Rationale
IX.A.7 Media	845-847	Current Text: "The media selected should be demonstrated to promote growth of USP <71> indicator microorganisms as well as representative isolates identified by environmental monitoring, personnel monitoring, and positive sterility test results" Comment: The current text is unnecessary. Proposed Revision: Delete "as well as representative isolates identified by environmental monitoring, personnel monitoring, and positive sterility test results".	Growth Promotion testing of compendial organisms is sufficient to demonstrate the viability of the media.
IX.A.8 Incubation and Examination of Media-filled Units	877-878	Current Text: "Each media-filled unit should be examined for contamination by personnel with appropriate education, training, and experience in microbiological techniques." Comment: For the inspectors (readers) of vials it is important to have regular eye examinations by an ophthalmologist. These should be mandatory for those who investigate the content of a contaminated vial. Provided that the inspectors are well trained and have a good understanding as to what they are looking for, this aspect is more important than having detailed experience in microbiological techniques. Any detected or suspect containers should be passed on for further detailed microbiological testing by an experienced microbiologist.	
IX.A.8 Incubation and Examination of Media-filled Units	878-879	Current Text: "There should be direct quality control unit oversight throughout any such examination." Comment: Does not reflect routine procedure. Proposed Revision: Delete sentence.	

Section	Guidance Line	Comment	Rationale
IX.A.8 Incubation and Examination of Media-filled Units	879-881	Current Text: "Clear containers with otherwise identical physical properties should be used as a substitute for amber or other opaque containers to allow visual detection of microbial growth."	We suggest that other approaches should be permissible as an occasional option for use if necessary, for example, transferring to clear containers for inspection after incubation. For some particular containers it may not be feasible to source a visually clear alternative.
IX.A.8 Incubation and Examination of Media-filled Units	888-893	Current Text: "After incubation is underway, any unit found to be damaged should be included in the data for the media fill run, because the incubation of the units simulates release to market". Comment: The handling of media fill containers does not simulate "release to market" Proposed Revision: "After incubation is underway, damaged units may be found (i.e., nonintegral). Any decision to exclude such incubated units (i.e., nonintegral) from the final run tally should be fully justified...."	
IX.A.8 Incubation and Examination of Media-filled Units	898	Current Text: Footnote [9] "To assess contamination risk during initial aseptic setup (before fill), valuable information can be obtained by incubating all such units that may be normally removed". Comment: Data would have no relevance or utility. Proposed Revision: Delete footnote	
IX.A.8 Incubation and Examination of Media-filled Units	904-906	Current Text: "The ability of a media fill run to detect potential contamination from a given simulated activity should not be compromised by a large-scale line clearance, which can result in removal of a positive unit caused by an unrelated event or intervention" Comment: The current text is contradictory. Proposed Revision: Delete clause	Elsewhere the guidance specifies that specific procedures for removal of units in production should be duplicated in process simulation.

Section	Guidance Line	Comment	Rationale
IX.A.9 Interpretation of Test Results	916-918	Current Text: "Video recording of media fill has been found to be useful in identifying personnel practices that could negatively impact the aseptic process." Comment: The phrase indicating that videotaping "has been found to be useful" may initiate an approach by investigators that will deem it mandatory. While videotaping may be useful in some cases, there are no real grounds for making it a requirement. The same function could be covered by the manual observation and assessment by experienced QC and Production personnel.	
IX.A.9 Interpretation of Test Results	935	Current Text: "When filling fewer than 5000 units, no contaminated units should be detected." Proposed Revision: Add: "One contaminated unit is considered cause for revalidation, following an investigation."	There is no guidance on the subsequent steps when the limit is exceeded, as there is for the other quantities.
IX.B Filtration Efficacy	1001-1002	Current Text: "Factors that can affect filter performance normally include (1) viscosity of the material to be filtered..." Proposed Revision: "Factors that can affect filter performance normally include (1) viscosity and surface tension of the material to be filtered,"	
IX.B Filtration Efficacy	1009-1010	Current Text: "The specific type of filter used in commercial production should be evaluated in filter validation studies." Comment: We suggest that text be added to clarify what "the specific type of filter" means. As stated, the phrase seems to mean the actual unit (e.g., exact cartridge/capsule). However, it is currently an accepted practice to test for retention using flat stock filter membranes. Proposed Revision: "The specific type of filter membrane used in commercial production should be evaluated in filter validation studies."	

Section	Guidance Line	Comment	Rationale
IX.B Filtration Efficacy	1027	Current Text: "We recommend you consider use of sterilizing grade filters in series; this is a common practice." Comment: Dual filtration is common practice. However, the word 'series' suggests two filters configured in one unit operation (Tank A - Filter 1 - Filter 2 - Tank B). Redundant filtration can also be performed using single filters in two successive unit operations (Tank A - Filter 1 - Tank B - Filter 2 - Tank C). Proposed Revision: "We recommend you consider use of redundant sterilizing grade filters; this is a common practice."	
IX.C Sterilization of Equipment and Container Closures	1033-1035	Current Text: "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 reasonable contamination potential exists" Comment: The current text presents unclear expectations. Proposed Revision: Delete sentence	Surfaces in the vicinity of sterile materials should not be required to be sterilized unless there is direct contact.
IX.C.1 Sterilizer Qualification and Validation	1050-1052	Current Text: "For both the validation studies and routine production, use of a specified load configuration should be documented in the batch records." Proposed Revision: "For both the validation studies and routine production, the load configuration should be documented in the batch records."	The use of maximum/minimum loads to qualify a range of loads is acceptable.

Section	Guidance Line	Comment	Rationale
IX.C.1 Sterilizer Qualification and Validation	1073-1075	Current Text: "The formal program providing for regular revalidation should consider the age of the sterilizer and its past performance. Change control procedures should adequately address issues such as a load configuration change or a modification of the sterilizer." Comment: We suggest that the testing schedule should be consistent, not dependent on age. If there are valid indications that the machine is unreliable or inconsistent, then it should not be in use. The effectiveness of the sterilizer should be established by validation, maintenance and routine review/assessment of cycle parameters. If there are concerns on reliability, they should be promptly addressed.	
IX.C.1.a Qualification: Empty Chamber	1081-1083	Current Text: "It is important that these studies assess temperature uniformity at various locations throughout the sterilizer to identify potential *cold spots* where there can be insufficient heat to attain sterility" Proposed Revision: "It is important that these studies assess temperature uniformity at various locations throughout the sterilizer."	In a porous load sterilization cycle, the variation of temperature will be minimal, and the identification of a 'cold spot' will be insignificant.

Section	Guidance Line	Comment	Rationale
IX.C.2 Equipment Controls and Instrument Calibration	1117-1118	Current Text: "The microbial count and D-valve of a biological indicator should be confirmed before a validation study." Comment: We suggest that text be added to clarify the meaning of "confirmed" in relation to D-values. If the D-value of an bioindicator must be exactly confirmed before use this would make it necessary to have specific testing devices (BIER vessels). This is not currently a GMP requirement. We suggest that a reasonable approach would be to verify the count and control the storage and use conditions. It should be acceptable to take the supplier's figure for the D value. An empirical kill/survival time test could be performed. We suggest that the approach be consistent with current Industry guidelines on steam sterilization.	
X.A.1 General Written Program	1152-1154 and 1170-1171	Current Text: "The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures." and "Critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing." Proposed Revision: (Line 1170)"Monitoring is not normally required on critical contact surfaces that have been sterilized. When performed, critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing".	• The purpose of environmental monitoring is to assess the conditions around the critical filling operation and adjacent support areas. The product-contact items should have been sterilized and this verified parametrically (sterilizer charts, etc) in conjunction with validation. Sampling these surfaces would effectively be a rudimentary test for sterility, and as such much less valuable than the sterilization monitoring data. • Elsewhere in the document it states that monitoring of critical surfaces is not mandatory.

Section	Guidance Line	Comment	Rationale
X.A.4.a Surface Monitoring	1247-1249	Current Text: "Environmental monitoring should include testing of various surfaces for microbiological quality. For example, product contact surfaces, floors, walls, ceilings, and equipment should be tested on a regular basis." Comment: It should not be necessary to test ceilings. Proposed Revision: "Environmental monitoring should include testing of various surfaces for microbiological quality. For example, product contact surfaces, floors, walls, and equipment should be tested on a regular basis."	The environmental monitoring should concentrate on realistic risk to product.
X.B Microbiological Media and Identification	1284-1286	Current Text: "Environmental isolates often correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for an investigation." Comment: The incidence of microbial recovery is low, and thus correlation back to media fills etc. is less likely. The most likely correlation is that the isolates are typically from personnel. Proposed Revision: "Environmental isolates may correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for an investigation."	
X.B Microbiological Media and Identification	1297-1298	Current Text: "Rapid genotypic methods are recommended for purposes of identification, as these methods have been shown to be more accurate and precise than biochemical and phenotypic techniques." Proposed Revision: Delete clause	We consider these recommendations to be too strongly suggested, as other techniques are adequate for the purposes of identification. Most QC laboratories are currently using alternatives and very few have the capability to perform genetic testing.

Section	Guidance Line	Comment	Rationale
X.E Particle Monitoring	1331-1332	Current Text: "A result outside the established specifications at a given location should be investigated." Comment: Environmental particulate values are not best classified by specifications; they have alert and action levels like other environmental monitoring. Proposed Revision: "A result outside the established action levels at a given location should be investigated."	
XI. Sterility Testing	1339	Current Section: "XI. Sterility Testing" Comment: The current section is unnecessary in this document. Proposed Revision Delete section.	
XI. Sterility Testing	1348-1352	Current Text: "If production facilities and controls are significantly better than those for sterility testing, the danger exists of mistakenly attributing a positive sterility test result to a faulty laboratory even when the product could have, in fact, been nonsterile. Therefore, some manufacturing deficiency may go undetected. We recommend the use of isolators to perform sterility testing." Comment: The current text is too restrictive. Proposed Revision: "We recommend the use of isolators or other suitably qualified areas and testing systems to perform sterility testing."	

Section	Guidance Line	Comment	Rationale
XI.A Choice of Methods	1363-1365	Current Text: "Study documentation should include evaluation of whether microbial recovery from inoculated controls and product samples is comparable throughout the incubation period." Proposed Revision: Delete clause	We suggest that the requirement to evaluate throughout the incubation period in order to show comparability throughout the incubation be deleted as it is in excess of compendial sterility test requirements.
XI.C Personnel	1377-1379	Current Text: "A written program should be in place to regularly update training of personnel and confirm acceptable sterility testing practices." Comment: We suggest adding text regarding the meaning of the term 'regularly' in order to be clear on the requirement. Since it is already a GMP requirement to keep training up-to-date, it is not clear as to whether this is an additional requirement.	
XI.D Sampling and Incubation	1395	Current Text: "• the batch processing circumstances – samples should be taken in conjunction with processing interventions or excursions" Proposed Revision: Delete clause.	• There is insufficient justification of the value in taking additional sterility samples for each intervention, and it would be impractical, especially when there is media fill data to support the intervention. • We suggest removing this sentence, as it is impossible to fulfill since firms are required to remove potentially contaminated units.
X.E.1 Identification (speciation) of the organism in the sterility test	1425-1426	Current Text: "Nucleic acid-based methods are recommended for microbial identification purposes." Proposed Revision: Delete clause.	We consider these recommendations to be too strongly suggested, as other techniques are adequate for the purposes of identification. Most QC laboratories are currently using alternatives and very few have the capability to perform genetic testing.

Section	Guidance Line	Comment	Rationale
XI.E.2 Record of laboratory tests and deviations	1441-1443	Current Text: "A sterility positive result can be viewed as indicative of production or laboratory problems and should be investigated globally since such problems often can extend beyond a single batch." Comment: We suggest that text be added to clarify the term 'globally', as many individuals have interpreted this term in different ways. It is unclear if 'globally' is regarded in the sense of across the whole operation at a particular site or 'globally' in the sense of across different sites worldwide.	
XI.E.2 Record of laboratory tests and deviations	1445-1446	Current Text: "To more accurately monitor potential contamination sources, we recommend you keep separate trends by product, container type, filling line, and personnel." Comment: This sentence is unclear. Proposed Revision: "To more accurately monitor potential contamination sources, we recommend you keep separate trends by product, container type, filling line and production, sampling and testing personnel."	
XI.E.2 Record of laboratory tests and deviations	1445-1449	Current Text: "To more accurately monitor potential contamination sources, we recommend you keep separate trends by product, container type, filling line, and personnel. Where the degree of sterility test sample manipulation is similar for a terminally sterilized product and an aseptically processed product, a higher rate of initial sterility failures for the latter should be taken as indicative of aseptic processing production problems." Comment: We suggest that since incidence is very low for failures in sterility testing, especially when using closed systems and isolators, it is not necessary to trend for each of the categories.	

Section	Guidance Line	Comment	Rationale
XI.E.2 Record of laboratory tests and deviations	1456-1458	Current Text: "Where a laboratory has a good track record with respect to errors, this history can help remove the lab as a source of contamination since chances are higher that the contamination arose from production." Comment: The conclusion based purely on good laboratory history is speculative and not very helpful. Even with a good laboratory history, mistakes can occasionally occur.	
XI.E.5 Product Presterilization Bioburden	1481	Current Text: "Trends in product bioburden should be reviewed (counts and identity)". Proposed Revision: Remove "identity"	During routine bioburden testing, only counts are measured. Identity is only determined if the bioburden exceeds the alert limit or at pre-determined intervals.
XII Batch Record Review: Process Control Documentation	1509-1510	Current Text: "All in-process data must be included with the batch record documentation in accordance with section 211.188." Proposed Revision: "All batch relevant data must be included with the batch record documentation in accordance with section 211.188."	• We suggest that only batch relevant data should be added to the batch record. We suggest that system relevant data may be evaluated separately and linked to batch release with no strict requirement to add them to the batch record. • Current text requires clarification. Environmental monitoring data is not routinely stored in batch records. Is this defined as in-process data?
Appendix 1 A.1 General	1546-1548	Current Text: "Although no isolator unit forms an absolute seal, very high integrity can be achieved in a well-designed unit. However, a leak in any certain components of the system can constitute a significant breach of integrity." Comment: The statements will mislead industry and investigators. Isolators are not designed to have or be "an absolute seal". Proposed Revision: Remove both of these statements from the Guideline.	An isolator is a positive pressure enclosure designed to maintain a higher pressure then the surrounding areas. This is analogous to a traditional clean room, where by the room pressure is higher then the areas surrounding it. A leak in the isolator or components does not automatically constitute a "significant breach" due to the positive pressure in the isolator system. The advantage of an isolator, is the removal of all direct human interaction from the product and process. A well designed maintenance program is the critical requirement to assure the isolator and components do not degrade and go unnoticed.

Section	Guidance Line	Comment	Rationale
Appendix 1 A.2 Glove Integrity	1556	Current Text: "A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity." Comment: A faulty glove does not immediately lead to a "critical breach of isolator integrity". Proposed Revision: "A faulty glove or sleeve (gauntlet) assembly represents a potential route of contamination."	The glove is a part of the whole aseptic process. Environmental monitoring, to include, air, surfaces and gloves should be utilized to determine the state of the aseptic process. Operators will enter the gloves with a sanitized glove over the naked hand. This creates a barrier between the operator's skin and the interior of a glove providing additional protection should a pinhole develop. The main emphasis of this paragraph should be the maintenance program. The remaining requirements in this paragraph state the critical aspects of an inclusive maintenance program.
Appendix 1 A.2 Glove Integrity	1562	Current Text: "Such a breach can be of serious consequence." Comment: The current text is misleading. Proposed Revision: Delete line	This statement lacks relevance, it will only serve to mislead industry and investigators. The term "can be" is too open for interpretation and may be applied as a requirement. As stated above, the gloves are one aspect in considering the state of control in the aseptic process.
Appendix 1 A.2 Glove Integrity	1565-1566	Current Text: "...the inner part of the installed glove should be sanitized regularly and the operator should" Comment: The current text is impractical. Proposed Revision: Delete clause	Sanitizing the inside of a glove would be difficult to perform efficaciously.

Section	Guidance Line	Comment	Rationale
Appendix 1 B.4 Clean Area Classifications	1611-1615	Current Text: "The classification of the environment surrounding the isolator should be based on the design of its interfaces (e.g., transfer ports), as well as the number of transfers into and out of the isolator. A Class 100,000 (ISO 8) background can be appropriate depending on isolator design and manufacturing situations." Proposed Revision: "The classification of the environment surrounding the isolator should be based on the design of its interfaces (e.g., transfer ports), as well as the number of transfers into and out of the isolator. A Class 100,000 (ISO 8 defined "at rest") background can be appropriate depending on isolator design and manufacturing situations."	For a closed isolator or an open isolator where mousehole environments have additional local protection and/or are validated not to entrain air, "Class 100,000 (ISO 8)" should be defined as in the "at rest" state in order to be harmonized with EU GMP grade D. We suggest adding text to incorporate definitions that are appropriate for both the EU and US. We foresee issues of interpretation between Europe and the US if there is no harmonization on this topic.
Appendix 1 D.2 Efficacy	1664-1666	Current Text: "For example, demonstration of a four-log reduction should be sufficient for introduction of controlled, very low bioburden materials into an aseptic processing isolator, including wrapped sterile supplies that are briefly exposed to the surrounding cleanroom environment." Comment: Only sterilized materials should be introduced into the aseptic processing isolator. Proposed Revision: "For example, demonstration of a four-log reduction should be sufficient for decontamination of material containers to be brought into an aseptic processing isolator, including wrapped sterile supplies."	
Appendix 1 D.2 Efficacy	1668	Current Text: "The uniform distribution of the defined concentration of decontaminating agent should also be evaluated concurrent with these studies (Ref. 15)."	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.

Section	Guidance Line	Comment	Rationale
Appendix 2 Blow-Fill-Seal Technology	1749-1751	Current Text: "The classified environment surrounding BFS machinery should generally meet Class 10,000 (ISO 7) standards, but special design provisions (e.g., isolation technology) can justify an alternate classification." Comment: For Blow-Fill-Seal applications, the text indicates particular requirements that are potentially in excess of current expectations. The environment in which BFS machine is located is indicated as Class 10,000. If interpreted as in operation, this is similar to EU grade B (EU GMPs require grade C). Also, there are requirements for endotoxin inactivation studies on the molding process that may be difficult to conduct.	
Appendix 3 Processing	1815	Current Text: "sterilyze" Proposed Revision: "sterilize"	Spelling
Appendix 3 Processing	1825	Current Text: "sterilyzed" Proposed Revision: "sterilized"	spelling
Appendix 3 A. Aseptic processing from early manufacturing steps	1851-1854	Current Text: "It is also important that process simulations incorporate storage of product or transport to other manufacturing areas. For instance, there should be assurance of bulk vessel integrity for specified holding times. The transport of bulk tanks or other containers should be simulated as part of the media fill." Comment: 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.	• 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. • 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.
REFERENCES	1874-1909	Proposed Revision: We suggest adding a reference to PDA Technical Reports 1, 2, 13, 22, 26, 28 and 36.	The PDA published Technical Reports are widely used in industry and provide substantially more complete information on the topics covered in this guidance.

Section	Guidance Line	Comment	Rationale
Glossary	1985-1986	Current Text: "Decontamination- A process that eliminates viable bioburden via use of sporicidal chemical agents." Comment: Current text is too specific. Proposed Revision: "Decontamination- A process that eliminates viable bioburden via use of sporicidal chemical agents or other means (i.e. UV light, etc.)."	