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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, RM 1061
Rockville, MD 20852

Re Docket No. 2003D-0382

Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing

PDA is pleased to provide these comments on the FDA Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing. PDA is an international professional association of more than 10,500 individual member scientists having an interest in the fields of pharmaceutical science, manufacturing and quality. Our comments were prepared by a committee of experts in the field of aseptic processing. These stakeholders are ready to work with FDA via PDA to develop a guidance for aseptic processing that would ensure quality products in the market place, which is the ultimate goal of both FDA and industry.

PDA acknowledges the effort made by FDA in the publication for comments of the FDA's Draft Guidance for Industry on "Sterile Drug Products Produced by Aseptic Processing" and wishes to recognize the improvements in this document from the previously published "Concept Paper."

We are pleased to offer our comments in order to further improve the document. We trust that our comments will be received as they were intended; that is, to strengthen the utility of the guidance that will be used by people with very diverse needs: ORA, Compliance, OPS, and the regulated industry.

Both industry and FDA urgently need this new guidance. The guidance should enable firms to know what to expect during FDA inspections of their aseptic processing areas and it should help ensure that FDA 483 observations are based on current guidance that is rooted in appropriate technology, science and best practices. However, some of the items in this guidance are covered in other guidance, and we would suggest that these items should be removed from this document. This document also makes reference to products and processes other than aseptic processing, and we would suggest clarification that this document does not apply to terminally sterilized products. We would also suggest the use of Internationally Standardized (SI) units throughout the document.

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Several recommendations may be unnecessarily specific and may prevent future technological advances because the solution is already prescribed in a FDA Guidance document. For example, specifics mentioned on lines 313, 373, 1510, 1042, and 1305

We welcome the concept described in line 1171 that reads, "Detection of microbial contamination on a critical site should not necessarily result in batch rejection." This concept is important and recognizes that individual values over the alert and action levels during environmental monitoring are not necessarily an indication of an out of control condition. It is important to note that environmental sampling of any surface is a test that neither confirms sterility nor indicates a lack of sterility assurance. Sampling activities themselves are aseptic interventions and the results of these activities are themselves uncertain. We ask that the Agency incorporate this concept in other sections of the document, such as:

1. Text in the Draft FDA aseptic processing guideline (see lines 132-137) suggests that cleanrooms used for aseptic processing should be evaluated under both as-built and static conditions, but that classification of the cleanroom should be conducted under dynamic conditions "with personnel present, equipment in place and operations ongoing." PDA recognizes that in part this does not reflect new policy from FDA. However, we believe that the position taken in the draft guideline has the potential to both require unnecessary cleanroom evaluation and to further blur the distinction between classification of cleanrooms and monitoring of their contamination control performance.

   PDA believes that classification of cleanrooms should be done primarily under static or as-built conditions as defined in ISO 14644 and that evaluation of the dynamic performance of a cleanroom should be left to the monitoring program. PDA suggests that recertification of the cleanroom on an annual or biannual basis is sufficient and that an assessment of clean room classification under "dynamic conditions on a routine basis" is unwarranted.

   It is inevitable that production operations will release relatively low levels of particulate contamination into the surrounding environment. The supply of components on conveyor systems, loading of component supply hoppers, vibratory bowl operations, and personnel movement can all result in intermittent or continuous particle generation or release. It is quite possible for there to be locations within a well controlled and carefully operated aseptic processing area that regularly exceed a particulate classification rating. The only way to prevent low level particulate generation of this kind would be to turn off the processing equipment, and completely eliminate personnel and their movement, neither of which are practical in a working manufacturing environment. PDA agrees that should changes to the operation of process equipment result in particulate counts that statistically exceed the process norm, investigation and possibly corrective action should occur. However, the observation of spikes during routine monitoring is not atypical and does not mean that the facility is operating outside of its classification nor does it imply that process control has been lost.

   It is also important to note that particulate measuring equipment has limitations in both accuracy and precision. Counting error may typically vary as much as +/- 20% of the mean.

FDA should take measurement limitations into account as well as the operational realities of processes and not expect or require industry to consider occasional excursions beyond the classification level to warrant investigation or corrective action. Rigorous control of aseptic processing environments is a goal both industry and FDA share, however standards and/or guidance that does not pragmatically consider both measurement error and actual manufacturing conditions is not helpful and only serves to create dissonance between guideline objectives and actual capability.

The wording in this section also implies that there can be a microbiological classification of cleanrooms. PDA agrees that it is normal industry practice to expect the incidence rate at which contamination is observed in cleanrooms to be well controlled and relatively constant. However, personnel release the vast majority of cleanroom contamination into the environment. Therefore, the areas of increased risk within a cleanroom will be those in which personnel are present and active. PDA realizes that scientists have published a correlation between particulate levels and microbial contamination (Reinmüller and Ljungqvist). However, in their studies the source of both total particulate and microbiological contamination was personnel. Therefore, PDA asserts that there is no value to requiring microbiological assessment of cleanrooms using the principles of total particulate classification. Microbiological assessment of cleanrooms is, in the view of PDA, strictly a monitoring exercise distinct and technically different from the assessment of the facility air supply, which is in fact an insignificant contributor of viable contamination.

2. The interpretation that single alert or action level excursions may constitute OOS may be an unintended consequence of Table 1. These are not absolute values. The document should clarify that microbial values have inherent variability. Sources of this variability include media, incubation time, incubation temperature, and adventitious contamination from personnel since samples are generally taken manually and aseptically.

3. PDA has stated in many previous responses to FDA policy on aseptic processing that actions including placing product on hold or rejection are not appropriate based upon single point excursions beyond suggested levels such as those in Table 1. We reiterate our view that it is inappropriate to require action as a result of tenuous and uncertain data. PDA does not believe that actions are appropriate unless the overall incidence of microbial recovery exceeds a firm's norm over a sampling period of sufficient time to conclude that a change in the state of control may have occurred. Investigations on single point excursions will result in reports that can draw no clear conclusion and which will not be useful in assessing actual risk

PDA would be pleased to offer our expertise to assist in the clarification of our comments, and the continued evolution of this important guidance. We look forward to working with FDA, industry and other professional associations to develop a world-class aseptic processing guidance document.

Acknowledgements:
PDA thanks the members of the Aseptic Processing Task Force for their input in developing these comments.

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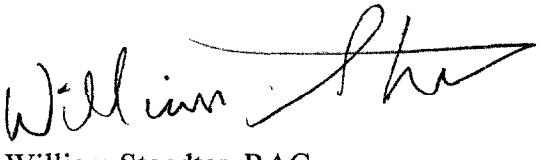
PDA thanks you again for the opportunity to comment on this draft guidance. If you require further information, please feel free to contact me via the information below.

Sincerely,



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Attachment: Comment Grid

Line Ref.	Comment
70	**Comment/Objection:** The sentence that reads: "There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization." Should be changed to exclude terminally sterilized products from this guidance. **Rationale:** 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. **Alternative Text:** 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*.
114	**Comment/Objection**: The sentence that reads "In such cases…" is a statement without guidance as to when such evaluation is required. **Rationale:** As stated in line 109 this guidance relates to CGMP issues and not how or why a product is developed. **Alternative Text:** Although this guidance document discusses CGMP issues relating to the sterilization of components, containers, and closures, terminal sterilization of drug products is not addressed. ~~It is a well-accepted principle that sterile drugs should be manufactured using aseptic processing only when terminal sterilization is infeasible. However, some final packaging may afford some unique and substantial advantage (e.g., some dual-chamber syringes) that would not be possible if terminal sterilization were employed. In such cases, a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility confidence.~~
136	**Comment/Objection**: The current sentence reads "The aseptic processing facility monitoring program should also assess conformance with specified clean area classifications under dynamic conditions on a routine basis." Does this mean routine environmental monitoring? **Rationale**: Statement is unclear **Alternative Text:** The aseptic processing facility's routine *environmental* monitoring program should ~~also~~ assess ~~conformance with specified clean area classifications~~ *the environment* under dynamic conditions. A single action level or alert level result at an identified location should not automatically require the conducting of an investigation. Multiple alert and action level results at an identified location should however prompt a formal investigation, based upon trend analysis."
152	**Comment/Objection:** Footnote 'e' states: "Samples … should normally yield no microbiological contaminants" is inconsistent with Table1 that sets the action level at 1 cfu. **Rationale**: Inconsistent Alternate text: Footnote 'e': ~~Samples … should normally yield no microbiological contaminants" is inconsistent with Table1 that sets the action level at 1 cfu.~~ *A target of no microbiological contaminants for samples from Class 100 (ISO 5) environments should be the goal. Occasional microbial counts may be acceptable with proper investigation.*

Line Ref.	Comment
167	**Comment/Objection:** The sentence that reads "Particles are significant because they can enter a product and contaminate it physically or, by acting as a vehicle for microorganisms, biologically (Ref. 2)." is not technically accurate. **Rationale:** Environmental particles are too small to "contaminate" a product physically. Visual and machine inspection would not detect the presence of these particles in the unlikely event they were to find their way into the finished product. **Alternate Text:** ~~Particles are significant because they can enter a product and contaminate it physically or, by acting as a vehicle for microorganisms, biologically (Ref. 2)."~~
174 304 310 Fn 7 969 976 2001 2049	**Comment/Objection:** Replace "micron" with "micro meter" throughout the document. **Rationale:** Harmonization **Alternate Text:** Replace "micron" with "micro meter"
183 & 1153	**Comment/Objection:** The term "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) work for 2.5 hours and take a break, work 2.5 hours and have a second break, 2.5 hours again for a third break is this one, two or three shifts? **Rationale**: To promote consistency **Recommended Definition:** A shift is a defined period of time where a group of personnel carry out scheduled work activities, as defined by the manufacturer.
192 & 338	**Comment/Objection:** The term "certification" is used inconsistently throughout the document. This term is used associated with qualification, classification and certification.
196	**Comment/Objection:** Delete the concept of point of use from the sentence "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

Line Ref.	Comment
	maintain unidirectional airflow during operations" and footnote 4 on page 6. **Rationale:** "Supplied at the point of use" is overly restrictive and the term "laminar" is incorrect. Unidirectional airflow in isolators may not be necessary or desirable; likewise the requirement to maintain 0.45 to 0.51 m/s velocity. **Alternate Text:** Delete footnote 4 and change sentence in line 198 to read: Air in critical areas should be ~~supplied at the point of use as~~ HEPA-filtered unidirectional ~~laminar~~ flow air at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations. 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
214	**Comment/Objection**: The sentence that reads "Air monitoring of critical areas should normally yield no microbiological contaminants" is inconsistent with Table1 that sets the action level at 1 cfu. **Rationale**: Inconsistent, Contradicts lines ***146-152 note c*** **Alternate text:** *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.*
238	**Comment/Objection**: The text that reads "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). "It should not be necessary to maintain any specific value, as long as a correct pressure cascade is maintained (as discussed in line241). **Rationale**: Unnecessary specificity. **Alternative Text**: ~~"For example, a positive pressure differential of at least 12.5 Pascals (Pa)[2] 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). *It should not be necessary to maintain any specific value, as long as the correct pressure cascade is maintained.*
243	**Comment/Objection:** The sentence that reads **"**Pressure differentials between cleanrooms should be monitored continuously throughout each shift and frequently recorded, and deviations from established limits should be investigated." is overly burdensome. **Rationale:** The requirement to frequently record values from a validated system that are within specification is overly burdensome and should be changed. Many monitoring systems take continuous readings ever few seconds from multiple

Line Ref.	Comment
	sites, 7 days a week, 24 hours a day. **Alternative Text:** 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.
249	**Comments/Objection:** The sentence that reads "For areas of higher air cleanliness, significantly higher air change rates will provide an increased level of air purification." might be misinterpreted and not always scientifically correct. **Rationale:** Higher air exchange rate dose not necessarily provide an improved air "purity" quality especially in a turbulent flow clean room. **Alternative Text:** *An adequate air change rate should be established for a non-unidirectional flow clean area. The air change rate should be based on the ~~particle generating~~ operations that will be performed in the area or other factors set by the manufacturer.* ~~Typically an exchange rate of 20 per hour is sufficient, but under high particle generation processes, such as Blow-Fill-Seal or capping operations, higher exchange rates may be needed to maintain the particle counts or other factors within specifications. For areas of higher air cleanliness, significantly higher air change rates will provide an increased level of air purification.~~
272	**Comments/Objection:** The sentence that reads "Sterilized holding tanks and any contained liquids should be held under continuous overpressure to prevent microbial contamination." Is too restrictive and does not recognize alternate approaches. **Rationale:** 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, including media fill data. **Alternative Text**: Sterilized holding tanks and any contained liquids should be held ~~under continuous overpressure~~ to prevent microbial contamination. ~~Safeguards should be in place to prevent a pressure change that can result in contamination due to back flow of nonsterile air or liquid.~~ *The use of overpressure or non-pressurized systems such as those utilizing 0.2 micro meter vent filters are acceptable when properly validated.* ~~via media fills~~. "
279	**Comment/Objection**: The sentence that reads "Filters should be integrity tested upon installation, and periodically thereafter (e.g., including end of use)." is not a common practice and requires increased human interventions, increasing the risk to maintain a sterile set-up. **Rationale**: These filters are integrity tested prior to installation and upon removal from use – they are not removed for integrity testing once in use. While in use, they are regularly monitored for viable and non-viable counts. Any excursion in counts would prompt an investigation which might include integrity testing. **Alternative Text**: ~~Filters should be integrity tested upon installation, and periodically thereafter (e.g., including end of~~

Line Ref.	Comment
	~~use).~~*Filters should be integrity tested prior to installation and prior to disposal as part of a preventative maintenance program. They should also be regularly monitored in use for viable and non-viable particles. Any excursions in monitoring should prompt an investigation that might include integrity testing.*
293	**Comment/Objection**: The sentence that reads "Among the filters that should be leak tested are those installed in dry heat depyrogenation tunnels commonly used to depyrogenate glass vials." is potentially dangerous. **Rationale:** The HEPA filters located in the heating zone of a hot air sterilizing tunnel are not there to sterilize the air passing through as the air has been heated to a sterilizing temperature (>300°C) prior to filtration. A particulate test should be performed, at normal cleanroom testing frequency, with the tunnel cold to determine the level of particulates that may be being shed from potentially heat degraded filter media. **Alternative text:** Among the filters that should be leak tested are those installed in the cooling zone of dry heat depyrogenation tunnels ~~commonly used to depyrogenate glass vials.~~ A particulate test should be performed in the sterilization zone, at normal cleanroom testing frequency, with the tunnel cold to determine the level of particulates that may be shed.
313	**Comment/Objection**: The sentence that contains "...a DOP challenge should introduce the aerosol upstream of the filter in a concentration ranging from approximately 25 to l00 micrograms/liter of air at the filter's designed airflow rating" should remove DOP reference, and not be specific as to challenge. **Rationale**: The mention of any specific challenge agent is too specific and could discourage technological advancements. The challenge should be sufficient to verify the filter's efficiency rating. **Alternative Text**: "a ~~DOP~~ challenge should introduce the aerosol upstream of the filter in a concentration ~~ranging from approximately 25 to l00 micrograms/liter of air~~ *sufficient to detect leaks ~~verify the filter's efficiency rating~~* at the filter's designed airflow"
326	**Comment/Objection**: The text that reads "HEPA filter leak testing alone is not sufficient to monitor filter performance. 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)." conveys that current industry practices are ineffective. **Rationale**: This statement implies that semi-annual velocity across the filter is not frequent enough when it is standard industry practice today. **Alternative Text**: "HEPA filter leak testing alone is not sufficient to monitor filter performance for ISO Class 5 areas. ~~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).~~ *It should be performed in conjunction with testing for ~~uniformity of~~ velocity (sufficient to demonstrate uni-directional airflow) across the filter on at least a semi-annual basis."*

Line Ref.	Comment
328	**Comment/Objection**: The sentence that reads "It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters)" is too vague. **Rationale**: What is meant by periodic? Change "periodic" to "semi-annual". **Alternative Text**: It is important to conduct ~~periodic~~ semi-annual monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters).
331	**Comment:** The sentence that reads "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." should not require measurements at the work surface. **Rationale**: Velocity "at a defined distance proximal to the work surface" is too vague to implement. The closer you get to any equipment or surface the more variable the data will be due to air changing direction due to influences of the surfaces, i.e. flat surface bounce back or proper flow away from product. Whatever location is chosen should be used over time so that velocity comparisons could be reasonably made. **Alternative 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."
348	**Comment:** (Spelling) sterility **Rationale**: Incorrect spelling **Alternative Text**: Use correct spelling of sterility
354	**Comment/Objection:** The sentence that reads "The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from an aseptic processing room and, most significantly, its critical area." might be misinterpreted. **Rationale:** This statement may cause confusion and lead less knowledgeable organizations, to add inappropriate items in the aseptic processing room or critical area. **Alternative Text:** The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from an aseptic processing room and, most significantly, its critical area. *However, caution must be exercised when designing an aseptic processing room or critical area to balance the need for limiting personnel movement and exits with the desire not to clutter the room or area with items only needed for exceptions.*
365	**Comment/Objection:** Replace the word "prefastened" with "preassembled". **Rationale**: The proposed term is better recognized and more descriptive.

Line Ref.	Comment
	Alternative Text: Rather than performing an aseptic connection, sterilizing the ~~prefastened~~ *preassembled* connection using sterilize-in-place (SIP) technology also can eliminate a significant aseptic manipulation.
373	**Comment/Objection**: The sentence that reads "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" does not recognize the potential of closed containers moving through higher classified areas. **Rationale**: A closed container can protect partially stoppered vials from adventitious contamination and the proposed text will harmonize the FDA guidance with Annex 1 paragraph 12 part 4. In addition, the current text is unnecessarily specific and may prevent future technological advances for the transport of partially closed containers from a fill line to a lyophilizer. **Alternative Text:** To prevent contamination, partially closed sterile product should be transferred only in critical areas *or closed containers by either transporting in a Class 100 (ISO 5) environment, with a Class 10,000 (ISO 6) background or in closed ~~sealed~~ transfer trays in a Class 10,000 (ISO 6) environment.*
403	**Comment/Objection**: The requirement that reads "With rare exceptions, drains are not considered appropriate for classified areas of the aseptic processing facility" is too broad. **Rationale**: Drains are appropriate in certain areas of higher classification, such as Class 100,000. **Alternative Text**: "With rare exceptions, drains are not considered appropriate for ~~classified areas~~ *Class 100 (ISO Class 5) areas through Class 10,000 (ISO Class 7)* of the aseptic processing facility"
432	**Comment/Objection:** The sentences that read "Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations. Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures and basic aseptic techniques during manufacturing operations." will create overly burdensome documentation in order to be complaint with the requirements specified. **Rationale**: The requirement is unclear as to frequency and documentation requirements and is too specific as to who should perform this evaluation. **Alternative Text:** *Operator's conformance to written procedures and basic principles of aseptic technique should be evaluated ~~periodically~~ during actual operations.*
452	**Comment/Objection:** The text that reads "Sterile instruments (e.g., forceps) should always be used in the handling of sterilized materials. Between uses, instruments should be placed only in sterilized containers. Instruments should be replaced as necessary throughout an operation. "is too prescriptive. **Rationale:** Instruments should be protected and maintained as sterile -- there are ways to do this besides placing in sterilized containers -- It is possible to sit them on sterilized surfaces in Class 100 air.

Line Ref.	Comment
	Alternate Text: Between uses, instruments should be *protected such that their sterility is not compromised, e.g.:* placed ~~only~~ in sterilized containers. Instruments should be replaced as necessary throughout an operation.
456	**Comment/Objection:** The dot point that reads "Keeping the entire body out of the path of unidirectional air." is too specific and does not provide adequate guidance. **Rationale**: Any intervention will result in disruption of unidirectional airflow. It is not practical to expect that there will never be the need for interventions. **Alternative Text**: ~~Keeping the entire body out of the path of unidirectional air.~~ *Personnel should minimize interventions into the critical zones. Such interventions can adversely disrupt the unidirectional air flow and should therefore be designed to minimize both the extent and frequency of occurrence.*
439 & 441	**Comment/Objection:** The dot point and subsequent sentence that reads "Contacting sterile materials only with sterile instruments. Sterile instruments (e.g., forceps) should always be used in the handling of sterilized materials." is too specific and does not provide adequate guidance. **Rationale**: Certain assembly and connecting of sterilized surfaces with sterile tools is impossible, i.e. assembling and fitting sterilized filling pumps is impossible with forceps. . **Alternative Text**: Sterile instruments (e.g., forceps) should always be used in the handling of sterilized materials *(Critical Surfaces). 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 (surfaces which subsequently have direct product contact) is to be avoided.*
472	**Comment/Objection**: The sentence that reads "Prior to and throughout aseptic operations, an operator should not engage in any activity that poses an unreasonable contamination risk to the gown." is too vague. **Rationale**: too vague and needs to be strengthened **Alternative Text**: "an operator should ~~not engage in any activity that poses an unreasonable~~ *be trained to minimize* contamination risk to the gown"
493	**Comment/Objection**: The sentence that states "Semi-annual or Yearly requalification is sufficient for automated operations where personnel involvement is minimized." conveys that current industry practices are ineffective. **Rationale**: Semi-annual requalification is not necessary when an effective personnel monitoring program is in place. **Alternative Text**: ~~Semi-annual or~~ Yearly requalification is sufficient for automated operations where personnel involvement is minimized. *Gowning requalification may be repeated based either upon adverse monitoring trends, issues raised in the*

Line Ref.	Comment
	change control program and/or on a timed basis such as annually.
537	**Comment/Objection**: The text that reads "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" over-simplifies this issue. **Rationale**: Only limited bioburden data for components subject to ~~overkill~~ validated sterilization is necessary. The term limit should be replaced with level to be consistent with other concepts in the document. **Alternative Text**: It is important to characterize the microbial content of each component that could be contaminated and establish appropriate ~~acceptance limits~~ levels based on information on bioburden. *Only limited bioburden data for components subject to validated sterilization cycles is necessary*."
551	**Comment/Objection:** The text that reads "If a component is not adversely affected by heat, and is soluble, it can be made into a solution and subjected to steam sterilization, typically in an autoclave or a fixed pressurized sterilize-in-place (SIP) vessel" is stating that a water soluble component (recipient or API) can be solubilized and steam sterilized during the product manufacturing process. **Rationale:** This should be included in the regulatory application and should not be included in this document. **Alternative Text:** Delete the clause ~~If a component is not adversely affected by heat, and is soluble, it can be made into a solution and subjected to steam sterilization, typically in an autoclave or a fixed pressurized sterilize-in-place (SIP) vessel~~
564	**Comment/Objection:** The text that reads "Parenteral products are intended to be nonpyrogenic. There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins." is too restrictive of applied to all components. **Rationale:** Few components (actives and excipients) used in parenteral products are derived from sources liable to be endotoxic, such materials of natural origin, starches sugars etc., but are chemically synthesized and therefore are of low natural bio/endo – burden. **Alternative Text:** Parenteral products are intended to be nonpyrogenic. There should be written procedures ~~and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins~~ *for the evaluation of components (active ingredients and excipients) for their potential to be contaminated with bacterial endotoxin. Where potential for contamination exists each received lot of material should be tested to appropriate specifications for acceptance or rejection. Any components failing to meet defined endotoxin limits should be rejected.*
565	**Comment/Objection**: "There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins" is too vague.

Line Ref.	Comment
	Rationale: Guidance beyond stating that products should meet their release criteria for pyrogen or endotoxin level. It should be left up to each firm to determine what degree of ingredient or in-process testing is required to achieve that goal. **Alternative Text**: *Incoming components (ingredients) should be accepted according to specifications included in the regulatory submission. Any components failing to meet defined specifications should be rejected.*
608	**Comment/Objection**: The text that reads "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." does not recognize the fact that many washers use the finial rinse's Water for Injection as the water for their initial rinses. **Rationale**: Many washers use recycled final rinse water for initial rinses. This water is not tested to meet Purified Water, USP. **Alternative Text**: At minimum, the initial rinses for the washing process should ~~employ~~ *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 for intermediate rinses is acceptable if validated.*
623	**Comment/Objection:** Delete sentence about approval of validation protocols and results: "The finished dosage form manufacturer is responsible for the review and approval of the contractor's validation protocol and final validation report". **Rationale**: This sentence implies that the finished dosage form manufacturer must formally approve protocols and reports, but more typically these will be reviewed without formal approval. In fact, many contractor's would not want other company personnel to approve their documents. **Alternative Text**: Delete sentence. ~~The finished dosage form manufacturer is responsible for the review and approval of the contractor's validation protocol and final validation report~~
629	**Comment/Objection:** The sentence that reads "A container closure system that permits penetration of air, or microorganisms, is unsuitable for a sterile product." is not technically correct. **Rationale**: This is not necessarily true of air. Some plastic 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. **Alternative Text**: A container closure system that permits penetration of ~~air~~ *microorganisms*, is unsuitable for a sterile product.
660	**Comment/Objection**: The sentence that reads "Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration." is too vague and needs an example. **Rationale**: not common practice.

Line Ref.	Comment
	Alternative Text: 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 endotoxins contamination.*
664	**Comment/Objection**: The text that reads "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." does not recognize the fact that many CIP systems use the finial rinse's Water for Injection as the water for their initial rinses. **Rationale**: Many CIP systems use recycled final rinse water for initial rinses. This water is not tested to meet Purified Water, USP. **Alternative 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. *The use of recycled WFI from the final rinse for intermediate rinses is acceptable if validated.*
664	**Comment/Objection:** Delete "...by validated cleaning procedures." **Rationale:** Clarification that prevention of endotoxin build-up is acceptable. **Alternative Text:** Replace this phrase with "...by validated endotoxin control procedures."
722	**Comment/Objection**: The following sentence "Media fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a worst-case approach." can be misinterpreted. **Rationale**: Stacking all potential worst-case situations into each media run does not represent an appropriate challenge simulating normal processing. **Alternative Text**: Media fill studies should simulate aseptic manufacturing operations as closely as possible. ~~, incorporating a worst-case approach. The~~ Media fill *studies* ~~program~~ should *be designed to* address applicable issues such as:
726	**Comment/Objection:** The sentence that reads "Factors associated with the longest permitted run on the processing line." is vague and should either be clarified or deleted.
727	**Comment/Objection**: The text in the dot point "number and type of normal interventions, atypical interventions, unexpected events (e.g., maintenance), stoppages, equipment adjustments or transfers" should not specify "number" **Rationale**: Number of typical interventions is proportional to the length of the operation. **Alternative Text**: ~~number and t~~Type of normal interventions, atypical interventions, unexpected events (e.g., maintenance), stoppages, equipment adjustments or transfers

Line Ref.	Comment
727	**Comment/Objection**: The text in the dot point "number and type of normal interventions, atypical interventions, unexpected events (e.g., maintenance), stoppages, equipment adjustments or transfers" should not specify "number" **Rationale**:"Unexpected" should be clarified. **Alternative Text**: ~~number and t~~Type of normal interventions, atypical interventions, ~~*anticipated and reasonably expected*~~ *infrequent permitted* ~~unexpected~~ events (e.g., maintenance), stoppages, equipment adjustments or transfers
739	**Comment/Objection**: The text in the dot point "operator fatigue" is unnecessary to be addressed during a normal media fill. **Rationale**: Environmental and personnel monitoring is a better assessment of operator fatigue; this should not be required for media fill. We are aware of no published data that correlate fatigue with increased contamination. **Alternative Text**: Delete line. ~~operator fatigue~~
757	**Comment/Objection**: "For example, the evaluation of a shift should address its unique time-related and operational features" is unclear **Rationale**: clarify or delete **Alternative Text**: For example, the evaluation of a shift *change* should address ~~its unique time-related and operational features~~ *the movement of personnel in and out of the aseptic processing and change rooms including de-gowning and gowning procedures.*
765	**Comment/Objection:** The sentence that reads " For example, facility and equipment modifications, line configuration changes, significant changes in personnel, anomalies in environmental testing results, container closure system changes or, end product sterility testing showing contaminated products may be cause for revalidation of the system." should remove the concept of significant changes in personnel. **Rationale:** Difficult to define and vague and changes in personnel are assessed in personnel qualification programs as defined by Section V Personnel Training, Qualification and Monitoring. **Alternate Text:** "For example, facility and equipment modifications, line configuration changes, ~~significant changes in personnel,~~ anomalies in environmental testing results, container closure system changes or, end product sterility testing showing contaminated products may be cause for revalidation of the system."
780	**Comment/Objection**: The text that reads "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" is inconsistent. **Rationale**: Elsewhere in this section the FDA specifies media fill sizes that are not representative of production duration.

Line Ref.	Comment
	This sentence is not consistent with PQRI recommendations on the 'Concept Paper' or PDA Technical Documents. The duration of the process simulation should be dictated by the time needed to prepare the required number of units and to include the activities to simulate necessary interventions. **Alternative Text**: Delete sentences. ~~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~~
784	**Comment/Objection**: The sentence that reads "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" is inconsistent. **Rationale**: Elsewhere in the document it mentions that atypical interventions may be rotated. **Alternative Text**: In any study protocol, the duration of the run and the overall study design should adequately mimic *appropriately designed* worst-case process operations. ~~conditions and cover all manipulations that are performed in the actual processing operation~~
795	**Comment/Objection**: The sentence that reads "For lyophilization operations, unsealed containers should be exposed to pressurization and partial evacuation of the chamber in a manner that simulates the process" is technically incorrect **Rationale**: Containers should not be exposed to 'pressurization' and exposed only to a slight vacuum to simulate that portion of the lyophilization cycle. **Alternative Text**: For lyophilization operations, unsealed containers should be exposed to ~~pressurization and~~ *a* partial evacuation of the chamber in a manner that simulates the process
822	**Comment/Objection**: The text that reads "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" is contradictory. **Rationale**: One sentence says that the range of speeds should be addressed, while the other specifies" worst case". **Alternative Text**: The media fill program should adequately address the range of line speeds (e.g., by bracketing all containers ~~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 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

Line Ref.	Comment
	conventional manufacturing processes ~~characterized by~~ allowing prolonged exposure<u>s</u> of the sterile drug product and container closures in the aseptic area.
837	**Comment/Objection**: The sentence that reads "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" is unnecessary and overly strict. **Rationale:** This statement is too vague and may lead to misinterpretation and lead to an expectation that HVAC systems may be expected to be operated at their worst case conditions e.g. high humidity, low differential pressure and low air exchange rate. The purpose of a media fill is not to validate the HVAC system, that is undertaken as a separate exercise. The purpose of a media fill is to ensure the critical interface of human operator and aseptic filling equipment can maintain an acceptable level of aseptic process integrity. **Alternative Text:** To the extent standard operating procedures permit stressful conditions, <u>*e.g. maximum number of personnel present and elevated activity level*</u>, it is important that media fills include analogous challenges to support the validity of these studies. <u>*Stressful conditions should not include reconfiguration of HVAC systems to operate at worst case limits.*</u>
844	**Comment/Objection:** "Use of anaerobic growth media (e.g., fluid thioglycollate medium) would be appropriate in special circumstances" is unclear. **Rationale**: All process gasses which come into contact with sterile materials must be filtered using a validated process. A media fill is not undertaken to validate sterilization processes but to assess the filling/closing process and the operator interactions in that process. Incorporating nitrogen, for example, in the media fill and then utilizing an anaerobic media will not optimize the capture of the types of organisms responsible for media fill contamination -aerobic organisms. **Alternative Text**: Delete Sentence. ~~Use of anaerobic growth media (e.g., fluid thioglycollate medium) would be appropriate in special circumstances~~
845	**Comment/Objection**: The text that reads "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." is unnecessary. **Rationale**: Growth Promotion testing of compendial organisms is sufficient to demonstrate the viability of the media. **Alternative 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~~.

Line Ref.	Comment
878	**Comment/Objection:** Remove the sentence "-There should be direct quality control unit oversight throughout any such examination." **Rationale:** Requiring the use of clear containers should not be an absolute requirement. Examination techniques which take advantage of special lighting conditions have been used successfully for examining containers for growth. Providing data which supports this means of examination should be sufficient. In other cases (ointments), contents are generally expressed from the container to facilitate examination of the filled units. A requirement for "direct quality unit oversight" should not be mandated. Provided that personnel have the appropriate education, training and experience or combination thereof should be sufficient. A statement that any suspect containers should be evaluated by the microbiologist adequately addresses the oversight role needed. **Alternate Text:** ~~There should be direct quality control unit oversight throughout any such examination.~~ *Containers used in the media fill should be the product containers or a suitable substitute. It is important to assure during the examination of media filled containers that contamination can be readily identified. Any suspect units identified during the examination should be brought to the immediate attention of the QC microbiologist.* ~~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.~~ .
904	**Comment/Objection**: The text that reads "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" is contradictory. **Rationale**: Elsewhere the guidance specifies that specific procedures for removal of units in production should be duplicated in process simulation. **Alternative Text:** Delete clause. ~~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.~~
920	**Comment/Objection:** The sentence that reads "The microorganisms should be identified to species level" is too specific. **Rationale**: It may not be possible to identify microorganisms to the species level. **Alternative Text**: The microorganisms should be identified to species level, *if possible*

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FN 9	**Comment/Objection**: Footnote 9 at the bottom of page 26 states "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." is not consistent with other sections of the document. **Rationale**: The media fill should simulate production practice. It has been FDA guidance for firms not to do testing "For Information Only". **Alternative Text**: Delete footnote. ~~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." is not consistent with other sections of the document~~
969 & 972	**Comment/Objection**: Incorrect usage of "porosity". **Rationale**: Pore size is the correct term; porosity is the ratio of filter void volume to total volume. **Alternative Text**: Replace "porosity" with *pore size*.
1009	**Comment/Objection**: The sentence that reads "The specific type of filter used in commercial production should be evaluated in filter validation studies" is technically not accurate. **Rationale**: The filter membrane is typically assessed in microbial retention studies, not the actual filter. **Alternative Text**: "The specific type of filter *membrane* used in commercial production should be evaluated in filter validation studies
1017	**Comment/Objection**: The text that reads "After a filtration process is properly validated for a given product, process, and filter, it is important to ensure that identical filter replacements (membrane or cartridge) used in production runs will perform in the same manner." is technically not accurate. **Rationale**: The filter membrane is typically assessed in microbial retention studies, not the actual filter configuration. **Alternative Text**: After a filtration process is properly validated for a given product, process, and filter *membrane*, it is important to ensure that identical filter *membranes be* ~~replacements (membrane or cartridge)~~ used in production runs will perform in the same manner."
1033	**Comment/Objection**: The sentence that reads "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." Is overly burdensome and may not be technically feasible. **Rationale**: Surfaces in the vicinity of sterile materials should not be required to be sterilized unless there is direct contact. **Alternative Text**: Delete sentence. ~~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" presents~~

Line Ref.	Comment
	~~unclear expectations...~~
1042	**Comment/Objection:** The sentence that reads "Sterility of aseptic processing equipment should be maintained by batch-by-batch sterilization. " is not technologically feasible for continuous processes. **Rationale:** This gets into the whole definition of what is a Batch? The requirement should center around validation. Sometimes it is better to leave things set up and keep running than to continually tear down and intervene. There are many applications approved by the FDA where this equipment is sanitized rather than sterilized. **Alternative Text:** ~~Sterility of~~ Sterilization / sanitization of aseptic processing equipment should *be performed at defined intervals (batch or campaign) and verified by periodic validation* ~~maintained by batch-by-batch sterilization~~.
1050	**Comment/Objection**: The sentence that reads "For both the validation studies and routine production, use of a specified load configuration should be documented in the batch records" is unnecessary. **Rationale**: The use of maximum/minimum loads to qualify a range of loads is acceptable. **Alternative Text**: For both the validation studies and routine production, ~~use of a specified~~ *the* load configuration should be documented in the batch records"
1165	**Comment/Objection**: The sentence that reads "Air and surface samples should be taken at the actual working site and at locations where significant activity or product exposure occurs during production" is not a good practice. **Rationale**: Air and surface samples should be taken at locations where significant activity or product exposure occurs during production. It is inadvisable to take samples at the "actual working site" because of the potential for introducing product contamination. **Alternative Text**: Air and surface samples should be taken ~~at the actual working site and at~~ locations where significant activity or product exposure occurs during production.
1073	**Comment: Objection:** Remove "age of sterilizer" from the following sentence "The formal program providing for regular revalidation should consider the age of the sterilizer and its past performance." **Rationale:** Decision to requalify is not age dependent. NOTE: Sterilizers need not be completely revalidated periodically; requalification is more appropriate based on performance, **Alternate Text:** ~~The formal program providing for regular revalidation should consider the age of the sterilizer and its past performance.~~ *The frequency of requalification should take into account factors such as past performance of the equipment, preventive maintenance, and change control program.*
1081	**Comment/Objection**: The text that reads "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" is not

Line Ref.	Comment
	always necessary. **Rationale**: In a porous load sterilization cycle, the variation of temperature will be minimal, and the identification of a 'cold spot' will be insignificant. **Alternative 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~~"
1117	**Comment/Objection**: The sentence that reads "The microbial count and D-value of a biological indicator should be confirmed before a validation study" should reflect that D-value may be accepted via certification. **Rationale**: D-value analysis may be accepted via certification as described in the USP 26, [55], [1035] and [1208]. **Alternative Text**: Delete requirement for D-Value determination. The new test should read. The microbial count ~~and D-value~~ of a biological indicator should be confirmed before a validation study" should reflect that D-value may be accepted via certification.
1170	**Comment/Objection**: The sentence that reads "Critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing." is inconsistent with other parts of the document. **Rationale**: Elsewhere in the document it states that monitoring of critical surfaces is not mandatory. **Alternative Text**: "*When performed,* c~~C~~ritical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing".
1207	**Comment/Objection:** The sentence that reads "A result at the action level should prompt a more thorough investigation." is too prescriptive. **Rationale**: Single occurrences at an action level do not necessarily indicate an out-of-control situation, as spurious action levels do inevitably occur. As such, the automatic carrying out of this type of investigation is non-value-adding, since it does not provide any concrete information upon which a decision can be made, and as such the investigation is likely to be inconclusive. Of much greater value is the presence of a number of action level occurrences at a specific location, which may exhibit an unfavorable trend. In this situation, trending provides more concrete information available on which to make a decision, and as such as investigation is more likely to be informative, and come to a firm conclusion which is indeed value-adding.

Line Ref.	Comment
	Alternative Text: ~~A result at the action level should prompt a more thorough investigation.~~ A single action level result at an identified location should not automatically require the conducting of an investigation. Multiple action level results at an identified location should however prompt a formal investigation, based upon trend analysis."
1224	**Comment/Objection:** The text that reads "The suitability, efficacy, and limitations of sanitization agents and procedures should be assessed. The effectiveness of these sanitization agents and procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces (i.e., via obtaining samples before and after sanitization) "does not reflect scientific literature that documents efficacy of many sanitizers. **Rationale**: There are copious data available in the literature to support efficacy of sanitizing agents. It should not be necessary for firms to continually repeat this testing. **Alternative Text**: ~~The suitability, efficacy, and limitations of sanitization agents and procedures should be assessed. The effectiveness of these sanitization agents and procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces (i.e., via obtaining samples before and after sanitization.~~ *The routine surface monitoring program provides ongoing support for the efficacy of the sanitization program.*
1229	**Comment/Objection:** The sentence reads "Upon preparation, disinfectants should be rendered sterile, and used for a limited time, as specified by written procedures" is too specific. **Rationale:** Line 1229 could be read as requiring sterilization post preparation. This effectively eliminates a common industry practice of purchasing sterile concentrated solutions and preparing, aseptically, use dilutions of sanitizing agents. Negates common and successful industry practice. What sense is there is filter sterilizing a solution that is self-sterilizing? **Alternative Text:** *Disinfectants should be purchased sterile, aseptically prepared from sterile concentrated solutions or subject to filter sterilization. It is not generally required to filter sterilize sporicides.*
1248	**Comment/Objection**: Remove "ceilings" from the sentence that reads "For example, product contact surfaces, floors, walls, ceilings, and equipment should be tested on a regular basis." because it is unnecessary. **Rationale**: Routine sampling of ceilings is unnecessary. **Alternative Text**: For example, product contact surfaces, floors, walls, ~~ceilings,~~ and equipment should be tested on a regular basis
1293	**Comment/Objection**: The sentence that reads ""~~At a minimum, the program should require species (or, where appropriate, genus) identification of microorganisms in these ancillary environments .....and to demonstrate that cleaning and~~

Line Ref.	Comment
	~~sanitization procedures continue to be effective)"~~ is too prescriptive. **Rationale:** The current text indicates that at a minimum the EM program should ID isolates from the less controlled environments, such as Class 100,000 (ISO 8) areas, to the species (or, where appropriate, genus) level at frequent intervals. The level of identification should be changed from identification to the species (or, where appropriate genus level) to "characterization" The requirement for an EM program that requires frequent identification of isolates from less controlled environments, such as Class 100,000 (ISO 8) areas, to the genus and species level is too great when evaluating the usefulness of the data obtained. Morphologically representative environmental monitoring isolates from lesser controlled environments, such as Class100,000 (ISO 8) areas, should be characterized. This pertains to the detection of isolate types obtained from samples that breach the action level as well as the periodic characterization of isolate types below the action limit. The information gathered from this activity is helpful in understanding the general types of organisms present and if the cleaning program needs to be adjusted. The intense amount of resources required to ID to the genus/species level does not provided added value in these areas over general characterization. The focus of genus/species identification should be placed on the samples taken closer to the aseptic operation. **Alternate Text:** ~~"At a minimum, the program should require species (or, where appropriate, genus) identification of microorganisms in these ancillary environments .....and to demonstrate that cleaning and sanitization procedures continue to be effective)."~~ *"At a minimum the program should require morphologically representative environmental monitoring isolates to be characterized. This pertains to the detection of isolate types obtained from samples that breach the action level as well as the periodic characterization of isolate types below the action limit."*
1297	**Comment/Objection**: Definitions are needed for "Rapid genotypic methods" and "phenotypic techniques" used in the sentence "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." **Rationale**: Biochemical, fatty acid methyl ester and other methods currently employed for microbiological identification are fit for purpose. The level of organism identification produced by current ID methods provides the information necessary for effective trending of contamination, product failure investigations and other studies. Overall, FDA overstates the importance of identification to species level in the manufacturing context. **Alternative Text**: Delete sentence. ~~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.~~

Line Ref.	Comment
1305 - 1307	**Comment/Objection**: The text that reads:" Total aerobic bacterial count can be obtained by incubating at 30 to 35°C for 48 to 72 hours. Total combined yeast and mold count is generally obtained by incubating at 20 to 25°C for 5 to 7 days." is too prescriptive and may inhibit the use of advanced technologies. **Rationale**: Incubation of EM samples for 5 to 7 days is longer than most firms currently incubate these samples While it is possible that longer incubation times could result in the recovery of some slower growing organisms, it is unlikely this would result in improved process control and it would further delay the availability of data for trend analysis. Also, the statement as currently written is not clear about requirements, for example, it should be possible to incubate a sample plate at one temperature and then shift it to another. Unless it is possible to temperature shift sample plates the FDA requirement as stated in the draft guideline would effectively double sampling requirements which would increase interventions in controlled areas and increase risk to the process. PDA does not think the relatively low probability that additional sampling or incubation time increases recommended in the draft guideline will increase process control, however could result in additional risk from sampling, will delay the availability of data and could substantially increase cost and incubation space requirements **Alternative Text**: ~~Total aerobic bacterial count can be obtained by incubating at 30 to 35°C for 48 to 72 hours. Total combined yeast and mold count is generally obtained by incubating at 20 to 25°C for 5 to 7 days~~.
1309	**Comment/Objection**: Definitions need to be provided for "Incoming lots of environmental monitoring media" and "prepared media" in the sentence that reads "Incoming lots of environmental monitoring media should include positive and negative controls. Growth promotion testing should be performed on all lots of prepared media." or the sentences need to be simplified. **Rationale**: GPT should be performed on each lots of EM media (prepared or not). **Alternative Text**: ~~Incoming lots of environmental monitoring media should include positive and negative controls. Growth promotion testing should be performed on all lots of prepared media.~~ Each lot of dehydrated or purchased-prepared media should include positive and negative controls. Negative controls are not required for terminally sterilized media. Where appropriate, inactivating agents should be used to prevent inhibition of growth by cleanroom disinfectants or product residuals (e.g., antibiotics).
1331	**Comment/Objection**: The sentence that reads "A result outside the established specifications at a given location should be investigated." is inconsistent with other parts of the document. **Rationale**: Environmental particulate values are not best classified by specifications; they have alert and action levels like other environmental monitoring. **Alternative Text**: A result outside the established ~~specifications~~ *action levels* at a given location should be investigated.
1339	**Comment/Objection**: The section entitled "XI. Sterility Testing" is unnecessary in this document,

Line Ref.	Comment
	Rationale: Why not refer to USP rather than creating a new section in a guidance document. The risk of inconsistency and the two documents staying in sync is high. **Alternative Text**: delete section.
1363	**Comment/Objection**: The sentence that reads "Study documentation should include evaluation of whether microbial recovery from inoculated controls and product samples is comparable throughout the incubation period" is included in USP. **Rationale**: Already covered in USP, and harmonized with EP/JP. **Alternative Text**: Delete clause. ~~Study documentation should include evaluation of whether microbial recovery from inoculated controls and product samples is comparable throughout the incubation period~~
1390	**Comment/Objection:** The text that reads "This limited sensitivity is why, for batch release purposes, it is important that an appropriate number of units are tested,[11] and that the samples uniformly represent: "is contradictory to USP. **Rationale**: There is potentially a serious legal issue here. FDA recognizes USP test methods as "official." The guidance, as written, seriously undermines this position. How many units are "appropriate"? **Alternative Text**: Delete sentence. ~~This limited sensitivity is why, for batch release purposes, it is important that an appropriate number of units are tested,[11] and that the samples uniformly represent:~~
1395	**Comment/Objection**: The text in the dot point that reads "the batch processing circumstances – samples should be taken in conjunction with processing interventions or excursions" is excessive. **Rationale**: 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. **Alternative Text**: Delete clause. ~~the batch processing circumstances – samples should be taken in conjunction with processing interventions or excursions~~
1424	**Comment/Objection**: Incorrect reference to USP. **Rationale**: Correction. USP uses Arabic numerals for volume numbers. The current volume is 26. **Alternative Text**: Replace XXV with 26.
1425	**Comment/Objection:** The sentence that reads ". Nucleic acid-based methods are recommended for microbial identification purposes." is overly burdensome. **Rationale:** As with lines 1297-1298 but using a different term FDA are recommending nucleic acid based methods of microbiological identification. **Alternative Text**: Delete sentence. ~~Nucleic acid-based methods are recommended for microbial identification purposes~~

Line Ref.	Comment
1445	**Comment/Objection**: The sentence that reads "To more accurately monitor potential contamination sources, we recommend you keep separate trends by product, container type, filling line, and personnel." is too prescriptive. **Rationale**: These requirements are too prescriptive and each firm much establish the type of trending that is appropriate for their production situation. This sentence is unclear and we believe it to mean production trends but the section is located in the laboratory section. **Alternative Text**: To more accurately monitor potential contamination sources, we recommend you keep separate trends by *appropriate categories such as,* product, container type, filling line and production, *sampling and testing* personnel.
1509 - 1511	**Comment/Objection:** Replace "included" with "reviewed" in the following sentence "All in-process data must be included with the batch record documentation in accordance with section 211.188." **Rationale:** Raw data might not always be part of the batch documentation **Alternate Text:** All in-process data must be ~~included~~ *reviewed* prior to batch release.
1547, 1556, 1682	**Comment/Objection/ Rationale**: 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. **Alternative Text**: *Breaches of integrity should be investigated. If it is determined that the product has been compromised, appropriate action shall be taken.*
1548	**Comments/Objections**: The sentence that reads "Replacement frequencies should be established in written procedures that ensure parts will be changed before they breakdown or degrade." has a requirement for replacement frequencies which is too vague. **Rationale**: Add text to be consistent with manufacturer's recommendations unless the firm has data to support something different. **Alternative Text**: Replacement frequencies should be established in written procedures *and consistent with manufacturers' recommendations unless the firm has data to support different replacement frequencies. Replacement frequencies should* ~~that~~ ensure parts will be changed before they breakdown or degrade.
1556 - 1565	**Comment/Objection**: The sentence that reads "Due to the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, the inner part of the installed glove should be sanitized regularly and the operator should also wear a second pair of thin gloves. " is impractical and may cause damage to the gloves.

Line Ref.	Comment
	Control of glove integrity should be consistent with the requirements in conventional clean rooms. **Rationale**: Sanitizing the inside of a glove would be difficult to perform efficaciously and could cause unpredictable adverse effects on the integrity of the glove. **Alternative Text**: Delete clause. ~~Due to the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, the inner part of the installed glove should be sanitized regularly and the operator should also wear a second pair of thin gloves~~
1587	**Comment/Objection**: "Sterilization" is used where "decontamination" is the correct term. **Rationale**: Correction **Alternative Text**: Replace "sterilization" with "decontamination".
1596	**Comment/Objection:** Replace "0.07 to 0.2 water gauge" with (Pascal) in the sentence that reads "Positive air pressure differentials from the isolator to the surrounding environment have largely ranged from approximately 0.07" to 0.2" water gauge" **Rationale:** This is too detailed; each isolator should have defined, validated differential pressure. **Alternate Text:** ~~Positive air pressure differentials from the isolator to the surrounding environment have largely ranged from approximately 0.07" to 0.2" water gauge~~ *The isolator shall be capable of operating within its specified differential pressure range under all operating conditions.*
1615	**Comment/Objection**: The sentence that reads "An aseptic processing isolator should not be located in an unclassified room" is unnecessarily strict. **Rationale**: As long as the area is controlled and the process validated, it should not require particulate air classification. Most conventional clean rooms have mouse holes that open directly into unclassified areas therefore the requirement for isolators should not be more restrictive. **Alternative Text**: Delete sentence. ~~An aseptic processing isolator should not be located in an unclassified room~~
1629	**Comment/Objection**: Delete "Some transfer ports can have significant limitations, including marginal decontaminating capability (e.g., ultraviolet) or a design that has the potential to compromise isolation by allowing ingress of air from the surrounding room. In the latter case, localized HEPA-filtered unidirectional airflow cover in the area of such a port should be implemented." **Rationale**: If the transfer ports are inadequate or cannot be appropriately decontaminated, they should not be used; hence there is no need for the deleted sentences.

Line Ref.	Comment
	Alternative Text: Delete sentence. ~~An aseptic processing isolator should not be located in an unclassified room~~
1648	**Comment/Objection**: The sentence that reads "For example, to facilitate contact with the sterilant, the glove apparatus should be fully extended with glove fingers separated during the decontamination cycle" is incorrect. **Rationale**: Incorrect usage. **Alternative Text** For example, to facilitate contact with the ~~sterilan~~ *decontaminant*, the glove apparatus should be fully extended with glove fingers separated during the decontamination cycle.
1664	**Comment/Objection**: The text that reads "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" is incorrect. **Rationale**: Only properly decontaminated materials should be introduced into the aseptic processing isolator. **Alternative Text**: "...four-log reduction should be sufficient for ~~introduction of controlled, very low bioburden materials~~ *decontamination of material containers to be brought* into an aseptic processing isolator, including the wrappers of sterile supplies ~~that are briefly exposed to the surrounding cleanroom environment~~..."
1749	**Comment/Objection**: The sentence that reads "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" is too limiting. **Rationale**: Many BFS machines are in less than Class 10,000 areas with good results. **Alternative Text**: The classified environment surrounding BFS machinery should generally meet Class ~~10,000 (ISO 7)~~ *100,000 (ISO 8)* standards, but special design provisions (e.g., isolation technology) can justify an alternate classification.
1802	**Comment/Objection**: The text that reads "It is critical that the operation be designed and set-up to uniformly manufacture leak-proof units" is not technically accurate. **Rationale**: No unit is "leak proof." **Alternative Text**: It is critical that the operation be designed and set-up to uniformly manufacture ~~leak-proof~~ *integral* units" is not technically acc
1812, 1824	**Comment/Objection**: Sterilyze should be *sterilize*. **Rationale**: Correction **Alternative Text**: *sterilize*

Line Ref.	Comment
2022	**Comment/Objection**: Delete the definition "Laminar flow- An airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight line vector." **Rationale**: This term is not used in the document, so it is unneeded in the Glossary. **Alternative Text**: Delete the definition: ~~Laminar flow- An airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight line vector~~.