Submission of comments on Revision of ‘Annex 1: Manufacture of Sterile Medicinal Products’

Comments from:

Name of organisation or individual
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1. General comments

1	General comment: The document is inconsistent in its use of references, they are present in some sections and absent in others. The document should include a comprehensive set of reference documents to support the points made in the text. This is especially important for those aspects of the draft that are most contentious.
2	General Comment: The document presents a view of sterile product manufacture inconsistent with that developed elsewhere as codified in regulations, international standards and pharmaceutical compendia. • For example, U.S. and Japanese guidance on sterile product manufacturing differ markedly from what is presented. • The cleanroom content in the draft does not conform to ISO 14644 and perpetuates the myths that clean rooms can be classified microbiologically and that microbiological testing can enhance sterility assurance. • USP chapters <1211>, <1228> and <1229> provide more contemporary and appropriate guidance for sterile product preparation. • There are also conflicts with current EMA guidance, e.g., the WFI Q&A paper and Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.
3	General Comment: Provide separate consideration of conventional cleanrooms, RABS and isolators because they are demonstratively different in many ways and considering them together denigrates isolator performance, elevates RABS capabilities and does not adequately consider the contamination risk in the far less capable barrier equipped conventional cleanroom.
4	General Comment: EMA's illogical and arbitrary insistence upon maintaining its Grade A/B/C/D system should be abandoned and the ISO 5 classification system used throughout the document. We have addressed these in some instances, but other citations to Grades A/B/C/D may remain as well as individual citations to Grade A, Grade B, and the unclear Grade A/B. Grades A, B, C, and D should be replaced with the corresponding classes of ISO 5, 6, 7 and 8. At the very least, all references to the arbitrary and confusing Grade B, and the totally undefined Grade A/B should be removed.
5	General Comment: Classification of controlled environments is limited to non-viable particle monitoring as described in ISO 14644. There are NO means to classify clean rooms based upon the microbial enumeration. The misguided ISO 14698 attempt to classify environments microbiologically should have no influence on this document. Any suggestion that environmental classification includes a microbial population requirement should be removed from the document.
6	General Comment: The document has a perspective on microbial monitoring that is inconsistent with scientific reality. The limit of detection for microbial testing is substantially higher than one (1) cfu, a level which is used throughout the document. This results in numerous misconceptions and overstatements regarding the value of environmental monitoring in the preparation of sterile medicinal products.
7	General Comment: The document frequently asks for testing of materials, containers, personnel environments and surfaces with the expectation that the testing can somehow assure quality. The founding principle of validation is that it can assure confidence in the reliability and appropriateness of the process in ways that testing can never provide.
8	General comment: The document needs better organization to place related content together. For example: environmental monitoring, terminal sterilization, barrier system and lyophilization content can be found in multiple locations. In addition, there is non-exact redundancy of content which only causes additional confusion, i.e., environmental monitoring, terminal sterilization.

Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
13-14	Comment: The statement lacks definition and direction because it doesn't point to the more important aspect of QRM in relation to sterile product manufacture which is Risk Mitigation. Assessment of risk is not enough: the document should explicitly support risk mitigation. Additionally, for consistency with that expectation, there should be no 'requirements' included in the document that potentially increase the risk of microbial, or particulate contamination of materials. Proposed change: … using the principles of Quality Risk Management (QRM) with emphasis on mitigation of risk at all times, …
14-15	Comment: The sentence is both redundant and potentially confusing. Deleting the extra words clarifies and broadens the objective of the document. Proposed change: … ensure that microbial, particulate and pyrogen contamination ~~associated with microbes~~ is ~~prevented~~ controlled in the final product.
17-22	Comment: This seems rather open-ended. When should the guidance be applied and to what extent? Considered important by whom? Application to other products not intended to be sterile is out of scope. Proposed change: Delete this section. It is out of scope.
46-48	Comment: Risk assessments do not accomplish anything without specific measures taken to reduce risk. Risk mitigation procedures are certainly possible but must consider statistical and analytical microbiological limitations. Proposed change: Risk assessments should include specific risk mitigation measures that ~~should be used to~~ justify alternative approaches to those specified in this Annex only if these alternative ~~approaches~~ risk mitigation measures meet or surpass the intent of this Annex and consider the statistical and analytical limitations inherent in microbial analysis of clean environments.
50-51	Comment: Clarify Proposed change: Combine text beginning at line 50 to read: "Quality Assurance is particularly important, and manufacture of sterile medicinal products must strictly follow carefully established and validated methods of manufacture and control. The QA program should consider all aspects of contamination control and its life cycle, with ongoing and periodic review and update as appropriate."

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
52-53	Comment: A "strategy" cannot assess the effectiveness of control and monitoring measures. An "effective program" of control and monitoring activities is what's required. Proposed change: ~~A contamination control strategy should be implemented across the facility in order to assess the effectiveness of all the control and monitoring measures employed. This assessment should lead to corrective and preventative actions being taken as necessary.~~ The strategy should consider all aspects of contamination control and its life cycle with ongoing and periodic review and update of the strategy as appropriate.
60	Comment: These might not be "successively linked" but may occur independently of each other or in parallel. Proposed change: "~~successively linked~~"
70	Comment: "(but not limited to)" is redundant. Proposed change: ~~"(but not limited to)"~~
72-106	Comment: The list of relevant concerns does not include the actual procedures used in support of the sterile manufacturing process. Given that these are predominantly manual, and thus less well controlled than many of the other items on the list, their omission is a serious error especially as personnel are understood to be THE major source of both variability and contamination in sterile product operations. This is a major omission. Proposed change: Add the following bullet item near the top of the list. Procedures utilized directly (i.e., formulation, assembly, sampling, equipment operation, etc.) and indirectly (i.e., cleaning, disinfection, monitoring, etc.) must be designed to minimize the risk of contamination). This includes those included in master production records, operating procedures, sampling and testing methods and others supportive of the sterile product manufacture. The list should also include product development, e.g., determining the manufacturing method(s) and sterilization technologies.
75	Comment: This bullet point lacks important details that require emphasis Proposed Change: Personnel – with emphasis on their proficiency in gowning, aseptic behaviour, aseptic assembly and, most critically, the specific interventional activities they are required to perform.
79, 81, 83	Comment: In many instances it is essential that the suppliers of API, raw materials, containers, closures and other critical items (sterilizing filters, single use disposables, gowning materials, etc) be subject to more than mere evaluation upon receipt. Quality agreements, periodic audits and other measures should be required where appropriate. The absence of such requirements is a serious shortcoming in the document. Proposed Change: Add content that addresses the importance of and specific measures to control the supply of critical items used in the manufacture of sterile medicinal products.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
86	Comment: The use of external laboratories is a major part of many smaller manufacturing sterile product operations. Add external laboratories to the specific outsourced services provided. Proposed Change: For outsourced services, such as laboratory analysis and sterilization, sufficient evidence should be provided to the contract giver to ensure they conform to the stated requirements.~~the process is operating correctly.~~
89	Comment: The stated activity – process risk assessment – is what this entire section of the draft is about. It shouldn't be listed as a subcomponent of itself! What could it possibly consist of that is not a part of this entire list? Proposed change: Delete the bullet point - ~~i) Process risk assessment.~~
91	Comment: This point bears both expansion and clarification. Proposed Change: ~~Process~~ Validation of sterilization, depyrogenation, cleaning, component preparation and production processes, utility systems and other systems contributing to the control of contamination.
94	Comment: Delete the later portion of this bullet items as ill-defined and lacking clarity. Proposed Change: ~~to a standard that will not add significant risk of contamination.~~
99-101	Comment: This bullet item suggests that there are available means to demonstrate 'sterility' or 'asepsis' through the use of expanded monitoring. While these methods can be of value, recognizing the analytical and statistical limitations inherent in them, expanding the application of these methods to enable detection of contaminants not currently found is scientifically incorrect. The environments used for sterile (aseptic) operations need not be and by in large cannot be 'sterile'. The conflation of the condition of asepsis with the concept of sterility is both semantically and scientifically erroneous. IT IS IMPOSSIBLE TO TEST STERILITY IN A PRODUCT OR ENVIONMENT USING ANY ANALYTICAL TECHNOLOGY. In addition, monitoring must never be invasive to the production processes in a manner that increases risk by adding activity in the critical zone. The increased interventional frequency that would result from continuous monitoring (whatever that means) entails excessive risk for no additional useful information gained. Proposed Change: Monitoring activities~~systems – including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination.~~ must not increase the risk of contamination ingress due to their proximity to critical activities.
104	Comment: While well intended, the last portion of this bullet suggests something which is not known to exist. Unless there is some specific guidance to offer it should be deleted. Proposed Change: …~~and the need for more robust investigational tools.~~

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109-110	Comment: Parametric release which is commonly employed for many terminally sterilized products would be considered unacceptable according to this sentence. It is the terminal sterilization process data that is considered in parametric release. As written this text prohibits any application of parametric release. Proposed Change: Sole reliance for sterility or other quality aspects must not be placed on any ~~terminal process or~~ finished product test.
114	Comment: The document is inexplicit regarding the references its authors consider it appropriate. In particular, this document clearly does not conform to the ISO 14644 – Controlled Environments standard (which it should), yet specific mention is made of ISO. It is noteworthy that many FDA and USP documents are also in conflict with this draft. It is inappropriate to have it both ways. By what right does EMA decide which standards are to be followed and which standards should be ignored as well as where harmonization should exist and where it should not? There is singular set of scientific principles used to develop standards; EMA should not ignore standards that are inconvenient to its premise, especially when those standards are objectively correct. Proposed Change: The document should explicitly state the reference standards which it follows. It should be extremely careful in proposing any practice, measurement or value inconsistent with accepted international standards.
127	Comment: The phrase "additional controls and measures" is unclear—additional with respect to what? Proposed change: Change "~~additional controls and~~stringent measures"
146-147	Comment: Risk assessment cannot monitor and detect contamination. Proposed change: Delete "~~to monitor and detect contamination.~~"
156-157	Comment: Processes cannot "ensure that medicinal products are stored and maintained in accordance with registered storage conditions." Proposed change: Processes associated with the finishing and transport of sterile medicinal products should not compromise the finished sterile product in terms of container integrity or pose a risk of contamination. ~~and ensure that medicinal~~ Sterile medicinal products are stored and accordance with registered storage conditions.
159 and 162	Comment: Clarify Proposed change: "medicinal products."~~medicines~~"
188-189	Comment: The wording "in such areas" is unclear. What are "such areas." Proposed change: "~~employed in such areas.~~"
203	Comment: the statement 'whilst unsupervised' is unclear. It does not fit with the rest of the sentence. Proposed Change: ~~whilst unsupervised'~~

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
203-206	Comment: The location of the monitoring is not specified at this point in the document. Table 6 includes expected levels for Grades A/B with different values for each. This implies that Grade A monitoring of personnel take place in Grade A. This is both impractical for the sites identified (see lines 199-200), and excessively risky. Monitoring of personnel in Grade A increases the potential for contamination ingress into that environment for the following reasons: a) personnel (the major source of contamination) are present in Grade A for longer periods, b) monitoring in Grade A increases activity in close proximity to sterile materials, and c) any added activity in Grade A increases contamination risk. Monitoring cannot confirm 'sterility' or 'asepsis' in any event, but there is absolutely no benefit to having this sampling performed in Grade A. Insistence on the Grade A personnel monitoring and consideration of risk should allow for that sampling to occur in Grade B adjacent to the Grade A environment with the Table 6 limits. For personnel working exclusively in Grade B, that monitoring can be performed upon exit from the aseptic core. Personnel monitoring should NEVER be performed in close proximity to sterilized materials. Proposed Change: Insert the following in line 206 –Grade A personnel monitoring should be performed in Grade B adjacent to the Grade A environment. For personnel working exclusively in Grade B, monitoring should be performed upon exit from the aseptic core.
205-206	Comment: Monitoring of personnel after each 'critical intervention' increases risk of contamination by requiring personnel extend their access within the critical zone to be monitored. Furthermore, there is no description provided in the document as to what constitutes a 'critical intervention' which would be required to interpret this statement. Monitoring after interventions attempts to do the impossible which is to link contamination to specific interventions, and it implies that detection of contamination means sterile products will be contaminated. Neither of these objectives are analytically possible. Monitoring is an intervention subject to microbial contamination independent of any process related interventional activity. Environmental monitoring in aseptic processing is already done far more intensely than is analytically or statistically warranted. Additional monitoring is not justifiable unwarranted as the actual limit of detection of the method is in the range of 10-100 cfu. We are already operating below the limit of detection of the method and additional environmental monitoring is unwarranted as it has no quantitative or qualitative meaning. Proposed Change: ~~This monitoring should take place immediately after completion of a critical intervention and upon each exit from the cleanroom.~~
207	Comment: The expectation for 'ongoing continuous monitoring' of personnel in Grades A/B is an expectation for a practice that exceeds current capabilities. There are no available means for continuous monitoring of personnel and if there were it would likely add to the risk of microbial contamination in critical environments. Proposed Change: It should be noted that there should also be ~~an ongoing continuous~~periodic monitoring program for personnel including some consideration of less frequent periodic monitoring under the supervision of the quality unit.

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210-215	Comment: This paragraph implies that personnel disqualification is solely caused by the operator, when there may be other contributing factors that result in their becoming contaminated. The proposed course of action is overly simplistic and ignores the need to review the environment, equipment and procedures surrounding the contamination events. Proposed Change: There should be systems in place for disqualification of personnel from entry into cleanrooms, based on aspects of the ongoing performance. ~~including ongoing assessment and/or the identification of an adverse trend from the personnel monitoring program~~. A comprehensive review of potential root causes for the contamination and corrective measures should be implemented. ~~Once~~ If disqualified, retraining and requalification is required before permitting the operator to have any further involvement in aseptic practices. This should include consideration of participation in a successful Aseptic Process Simulation (APS).
218	Comment: The document lacks clarity. Proposed Change: Change ~~such~~ appropriate
223-225	Comment: Personnel should . . . "report any specific health conditions or ailments which may cause the shedding of abnormal numbers or types of contaminants and therefore preclude clean room access." How would they know these specific health conditions or ailments? Proposed change: ~~specific health conditions or ailments~~ illnesses for supervisory evaluation.
230-234	Comment: This is an extreme expectation. It could easily be interpreted to preclude microbiological laboratory personnel from entering the aseptic area. The prohibitions also ignore other potential contamination sources: employees that own pets; employees that have ill family members at home; employees that live on or near farms, etc. Extending the prohibition to these circumstances is excessive. The applied procedures, gowning methods and controls must be adequate to accommodate all potential situations extending to aspects other than illness. Proposed Change: Staff ~~who have been engaged in the processing of human or animal tissue materials or of cultures of micro-organisms, other than those used in the current manufacturing process, or any activities that may have a negative impact to quality, e.g. microbial contamination,~~ should not enter sterile product areas unless rigorous, clearly defined and effective entry procedures have been followed. Staff having systems of illness including coughing, nasal congestion or drainage, or clinically significant fever should be excluded from aseptic clean rooms
236-237	Comment: The prohibition on cell phones should not extend to areas outside the aseptic core. That restriction should only apply to aseptic areas. Proposed Change: Wristwatches, make-up and jewelry and other personal items ~~such as mobile phones~~ should not be allowed in clean areas. ~~Wristwatches, make-up and jewellery and other personal items such as mobile~~ Mobile phones should not be allowed in aseptic ~~clean~~ areas.
243	Comment: There are no widely available and effective eye coverings that are sterilized. Proposed Change: … garments are sterilized and eye coverings are ~~have been~~ sterilized / sanitized …
260-261	Comment: "They should shed virtually no fibres or particulate matter." As many gowning systems include fabrics and components made of fibres and their cleaning cannot be considered absolute for removal of potential foreign matter the expectation is excessive. Proposed change: Modify the test to add - "They should ~~not shed fibres or particulate matter~~ be made of suitable materials that do not compromise the area classification."

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
264	Comment: Excessive detail which may not be appropriate for all aseptic gowning designs. Proposed Change: Sterile ~~headgear~~ attire should totally enclose hair and facial hair; ~~it should be tucked into the neck of the sterile suit; a sterile face mask and sterile eye coverings should be worn to cover all facial skin and prevent the shedding of droplets and particles.~~ Appropriate sterilized, ~~non-powdered rubber or plastic~~ gloves and ~~sterilized~~ footwear should be worn. ~~Trouser legs should be tucked inside the footwear and garment sleeves into the gloves.~~ The protective clothing should minimally shed ~~virtually no~~ fibres or particulate matter and retain particles shed by the body. Garments should be packed and folded in such a way as to allow operators to change into the garments with contact to the outer surfaces of the garment reduced to a minimum.
268-269	Comment: "The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body." This is not possible with conventional aseptic area clothing systems. See Ljungqvist and Reinmueller. Proposed change: Change to read "The protective clothing should not ~~shed fibres or particulate matter that could~~ compromise the area classification and be designed to retain particles shed by the body."
277	Comment: The guidance reflects practices that are not widespread. Proposed Change: … that facility suits, ~~including dedicated socks~~ be worn before …
282	Comment: Unclear. It is not enough to "provide" clothing. Proposed change: Delete "~~provided~~worn"
283-284	Comment: The last sentence is redundant. Proposed Change: ~~Garments and gloves should be changed at least for every working session.~~
288	Comment: The guidance is overly prescriptive and there is no clarity as to what is meant by 'separate' laundry facilities. Proposed Change: ~~Separate laundry facilities for such clothing are desirable.~~
296	Comment: Wording unclear. The word 'strict' has no specific meaning in this sentence. Proposed change: Delete - should adhere to ~~strict~~ aseptic technique at all
300	Comment: Wording unclear. Temperature and humidity settings cannot prevent shedding. Proposed change: Replace "~~prevent~~minimize"
311-312	Comment: Wording unclear. Proposed change: Change to read ". . . carried out using technical and operational designed to control contamination within the clean area.
321	Comment: The use of unidirectional air flow in isolators provides no operational advantage over turbulent air. Years of experience in sterility test isolators where extensive manual activity is required have not demonstrated any contamination problem that could be resolved by the use of unidirectional air flow. Further, laminar air flow is a misnomer as truly laminar air flow does not exist in any clean room or separative technology environment. The document establishes expectations which cannot be objectively evaluated or established. Proposed Change: …, such as provided in unidirectional laminar air flow work stations ~~or isolators~~.

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321-323	Comment: There is no basis for the cited air velocity range. Unidirectional flow can be established above and below the arbitrary range included in the draft. See Mason, W., et al, "Working Height Velocity Measurement in Conventional Cleanrooms, *Pharmaceutical Engineering*, July/August 2009, online at www.ispe.org/PE. Isolators because of the completeness of their separation do not require the same air velocities as conventional cleanrooms or RABS designs. Air velocities in isolators can be substantially less and non-unidirectional. Proposed Change: Unidirectional air flow systems should provide a homogeneous air flow over exposed sterile materials.~~speed in a range of 0.36 – 0.54 m/s (guidance value), the point at which the air speed~~ Air velocity measurements ~~is taken~~ should be ~~clearly justified in the protocol~~ taken to define the operating condition, however in isolator enclosures or other low volume work areas air velocities can be considerably lower than is customary for manned clean rooms. Unidirectional air is not required in isolators.
325	Comment: There are no reliable and reproducible means to measure air velocity at work height. The most appropriate approach is to measure the air velocity proximate to the filter face. Airflow near the work surface is typically impeded by the presence of an equipment surface oriented perpendicular to the direction of air movement. These conditions render air velocity measurements close to the work surface non-reproducible and thus meaningless. Proposed Change: During initial qualification and requalification air ~~speeds~~ velocitiy should ~~may~~ be measured ~~either~~ close to the terminal air filter face ~~or at the working height,~~.
331-332	Comment: This sentence properly defines the desired objective of minimizing human activity within the Grade A zone. This contrasts with expectations for personnel monitoring in Grade A that mandate monitoring after interventions. Considering that the 'perfect' intervention is one that is not performed, the perspective stated here should be followed, and the document adjusted elsewhere to conform to it. Proposed Change: These comments include recommendations for minimizing human intervention in ISO 5 at the appropriate points throughout the document.
351	Comment: "Materials liable to generate fibres should not be permitted in clean areas." This would eliminate the majority of aseptic gowns, hoods and foot covering, as well as face masks which are widely used in clean and aseptic environments. Proposed change: ~~Materials liable to generate fibres should not be permitted in clean areas.~~
353	Comment: It's not just "false ceilings" that could be a problem. Proposed change: Delete ~~"false"~~
358	Comment: Traps do not prevent backflow. They provide a means for air and condensate removal in one direction, but are not designed or capable of preventing backflow. Proposed change: Change to read "should be designed to prevent backflow."
365-366	Comment: Exit airlocks are the exception, and the suggested revised text provides for this. Proposed change: Replace "same grade as the cleanest area into which it connects ~~leads~~"
400	Comment: ULPA filters have no practical value in either manned cleanrooms or unmanned isolators. HEPA filters have proven satisfactory for these systems for many years. Proposed change: A HEPA ~~or ULPA~~ filtered air

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415	Comment: Grade B air is specifically indicated in this document as being other than unidirectional. Proposed Change: Air flow patterns should be visualised in grade A~~/B~~ areas to evaluate if airflow is unidirectional.
433	Comment: The document uses the term barrier in a manner which fails to distinguish between highly capable technologies such as isolators which are among the most capable of current aseptic processing technologies; and less capable designs such as open RABS, and simple curtain / partial barriers designs. Open RABS systems allow interventions similar to those required in manned clean rooms and are substantially less effective in achieving full personnel separation as compared to isolators or closed RABS. To treat these varying capability systems together as is done throughout the document is to equate their performance which is substantially different. The text could be substantially improved by separate treatment of isolation technology and RABS (open and closed) technologies, and make the distinction between those designs and ordinary manned cleaned rooms the majority of which rely on some form of minimally effective barrier. Proposed Change: Provide separate consideration of conventional cleanrooms, RABS and isolators because they are demonstratively different in many ways and considering them together denigrates isolator performance, elevates RABS capabilities (especially for open RABS designs) and implies that the far less capable barrier designs used in conventional cleanrooms are their equal.
437-439	Comment: This content creates the impression that transfer of materials into isolators or closed RABS is inherently more risky than transfers into clean rooms. Even if one did nothing more than wipe materials down with a disinfectant and place them in an airlock for a defined residence time isolators will still be a lower risk than clean rooms! Proposed Change: Provide content that supports the clearly superior performance of isolators and closed RABS. Make it clear that open RABS and conventional manned cleanrooms are decidedly less capable.
439-442	Comment: This sentence suggests that both isolators and RABS should be sterilized. This is possible, albeit unnecessary, in an isolator, which can generally be automatically decontaminated to provide appropriate conditions for aseptic processing. RABS systems, aside from those that employ isolator type design concepts, cannot be sterilized and their decontamination may be less capable than those used for isolators. It is extremely difficult to alter the existing combined text into guidance that treats the different technologies in a clear manner. There is a significant difference between decontamination and sterilization, and clarity needs to be given to that difference as well. The common means for introduction of materials into isolators does not require the background environment to be of higher grade. Depending upon the design of the RABS and how the materials are introduced (especially where doors must be opened), higher grades may be required. This is another instance where combined treatment of isolators and RABS fails in the document. Proposed Change: The transfer of materials into and out of the RABS or isolator is ~~one of the greatest~~ a potential sources of contamination and therefore the entry of additional materials following their decontamination must be avoided unless managed through an RTP system or double door decontamination system~~sterilisation should be minimized~~. Add content on decontamination to clarify the expectation.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
443-447	Comment: This paragraph summarizes practices necessary for the successful operation of isolators and RABS and suggests that they require additional considerations beyond that associated with conventional cleanrooms. The same concerns articulated in this paragraph apply equally to conventional cleanrooms. The guidance provided is appropriate to all technologies used for the production of sterile medicinal products including BFS and FFS and provided throughout this document. This paragraph thus serves no useful purpose other than to restate considerations that all sterile manufacturing technologies must provide. Proposed Change: ~~The design of the RABS or isolator shall take into account all critical factors associated with these technologies, including the quality of the air inside and the surrounding area, the materials and component transfer, the decontamination, disinfection or sterilization processes and the risk factors associated with the manufacturing operations and materials, and the operations conducted within the critical zone~~.
449-450	Comment: There is no documented evidence that the use of unidirectional air flow provides any benefit in isolation technology, whereas that is a required component for RABS systems. As noted above discussing isolator and RABS technologies independently would improve the document substantially. This same content needs to be provided for conventional manned cleanrooms as well. EMA's illogical and arbitrary insistence upon maintaining its Grade A/B/C/D system should be abandoned and the ISO 5 classification system used throughout the document. Proposed Change: The critical zone of ~~the~~ conventional manned cleanrooms and RABS ~~or isolator~~ used for aseptic processes should meet ~~Grade A~~ ISO 5 with unidirectional air flow. The critical zone of isolators used for aseptic processes should meet ISO 5.
450-451	Comment: Excessive requirement for isolators included as there is no documented evidence that unidirectional air improves isolator performance in any configuration. Proposed Change: ~~Under certain circumstances~~ Turbulent airflow may be justified in an ~~closed~~ isolator when proven to have no negative impact on the product.
453-454	Comment: The use of negative pressure for an aseptic processing isolator should be considered only where the risk to the operator or the environment is extreme and cannot be sufficiently mitigated by other means. Negative pressure isolators for aseptic processing should be avoided unless there is NO other means to mitigate operator exposure to materials. The text provided is not strong enough on this point. Proposed Change: … negative pressure isolators should only be used for aseptic processing when containment of the product to maintain operator safety cannot be adequately mitigated by other means.~~is considered essential.~~
456-458	Comment: The guidance is inadequate to secure the safe operation of RABS systems especially those that are opened during aseptic processing. The provided guidance for air supply for a RABS with open doors during interventions is inconsistent with FDA expectations. Proposed Change: For RABS that can operate with doors closed at all times following decontamination, the background environment should meet ISO 6 ~~grade B~~. For ~~open~~ RABS that require the doors to be opened after decontamination~~, or where doors may be very rarely opened during processing~~, the background environment should meet ISO 5 ~~grade A~~ and studies should be performed to demonstrate the absence of air ingress.

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460-461	Comment: This sentence contradicts the content included at lines 465-466 which allows for greater flexibility in the background environment. Proposed Change: ~~For open, positive pressure isolators or closed isolators with decontamination by a sporicidal agent, the surrounding area should correspond to a minimum of grade D~~. ~~The disinfection regime should be included as a key consideration when performing the risk assessment to design the contamination control strategy for an isolator.~~ The second sentence should be relocated to the next section of the document.
465-470	Comment: Revised to include a portion of the content from the previous section after deleting the initial sentence because it is contradictory to this section. The last sentence is erroneous because material entry in isolators and RABS (especially open RABS) can be substantially different. See the earlier comment at line 437-439. Proposed Change: For isolators, the required background environment and its decontamination regimen can vary depending on the design of the isolator, its application and the methods used to achieve bio-decontamination. The decision as to the supporting background environment should be documented in a risk assessment where additional risks are identified, such as for negative pressure isolators. Where items are introduced into RABS (especially open RABS designs) ~~to the isolator~~ after decontamination ~~disinfection~~ then a higher grade of background should be considered.
472	Comment: There is no content provided relative to the gloves installed on RABS, which require aseptic installation subsequent to sterilization. This is a further example of the need to separate the isolator and RABS content in this guidance. Additionally, most isolator gloves are now made of Hypalon and its generic equivalents and are very puncture resistance. This may not be the case with all gloves. Proposed Change: Content related to glove integrity, sterilization / decontamination, installation and leak testing differ for isolators and RABS. Separate treatment of these issues and technologies is essential to make this document fully useful.
472-478	Comment: This content is confusing as it is unclear whether the guidance is directed towards isolators, or both isolators and RABS. As noted earlier at Line 433, separate content is necessary to address the similar but different concerns associated with the different technologies. Proposed Change: Provide separate content for isolators and RABS on this subject.
474	Comment: There are no means to establish the integrity of RABS which rely on air overspill to afford separation between the interior and exterior of the enclosure. This is another reason for the recommendation to separate the content.
476-478	Comment: Integrity testing of incomplete barriers as used in conventional cleanrooms and RABS is impossible. Integrity and leak testing after each intervention is an unrealistic expectation. The document does not address RABS which do not lend themselves to leak testing for other than gloves. Testing gloves prior to use on a RABS has multiple adverse consequences: contamination of glove surfaces during the leak testing; additional activity adjacent to the critical zone; and potential damage to /weakening of the gloves as a consequence of the leak test. Proposed Changes: ~~Integrity testing of the barrier systems and leak~~ Leak testing of ~~the~~ isolators and ~~the~~ isolator / RABS gloves ~~system~~ should be performed using visual, mechanical and physical methods. They should be performed at defined periods, at a minimum ~~of~~ the ~~beginning and~~ end of each batch~~, and following any intervention that may affect the integrity of the unit~~. The limits for leak tests should be derived from a formal risk assessment.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
480-481	Comment: Decontamination procedures for isolators can be validated; however there are no means to accomplish that directly for decontamination processes used for RABS. The proposed changes do not address the appropriate measures necessary for RABS. Another reason for separate treatment of the technologies. Proposed Changes: Decontamination processes of an isolator ~~or RABS~~ should be validated and controlled in accordance with defined parameters. Add content specific to RABS decontamination.
485	Comment: There is no definition of what a 'clean air device' is. Proposed Change: Clean rooms, RABS, and isolators ~~and clean air devices (clean areas)~~ for the manufacture of products should be qualified according to the required characteristics of the environment.
493-495	Comment: The content is correct; however its placement after content that discusses 'environmental cleanliness level in the operational state' suggests that classification can be accomplished in the operational state. Classification of environments is restricted to 'at rest' or static conditions as stated in ISO 14644. It is not scientifically possible to classify an environment microbiological the growth based methods used for such purposes have a limit of detection between 10-100cfu and are statistically and analytically incapable of classifying an environment. Proposed Change: Relocate this content to follow Lines 497-499. Additions / edits are made to the text as well. Note: Classification is a method of assessing the level of air cleanliness against a specification for a cleanroom ~~or clean area device~~ by measuring the airborne particle concentration. The classification is part of the qualification of a clean area and is performed under 'at rest' or static conditions..
497-498	Comment: There is no definition of what a 'clean air device' is. Proposed Change: Clean rooms, RABS, and isolators ~~and clean air devices~~ should be …
501-503	Comment: Classification cannot be performed under operational conditions. See ISO 14644. Any measurements taken under operational condition are monitoring and subject to variations associated with the activities being performed. Since this section of the document focuses on qualification, there should be no mention of monitoring or dynamic conditions. Proposed Change: For classification, the airborne particles equal to or greater than 0.5 µm should be measured. This measurement should be performed ~~both~~ in the 'at rest' condition~~and in operation~~. The maximum permitted airborne particle concentration for each grade is given in table 1.
505	Comment: As operational measurements are not classification; the content of Table 1 should be revised. All mention of 'in operation' values should be removed and the column with the 'in operation' values deleted. Proposed Change: Table 1: **Maximum permitted airborne particle concentration during classification** Right hand column heading: ISO classification ~~in operation/~~at rest

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
505	Comment: The A, B, C, D table should be deleted as it is irrelevant and useless. Proposed Change: ~~Grade A~~ ISO 5 'at rest' – It is time to sunset the A, B, C, D system which is of no value. EMA should harmonize with ISO 14644. The expectation of microbiological classification of clean rooms is statistically and analytically incorrect.
507-508	Comment: As classification is only possible in the 'at rest' state the inclusion of this note is irrelevant. Proposed Change: ~~For grade D, no "in operation" limits are defined; the company should establish in operation limits based on a risk assessment and on historical data, where applicable.~~
515-517	Comment: The advice provided suggests classification under the operational state. Proposed Change: ~~For later stages of qualification and classification, such as performance qualification, locations should be based on a documented risk assessment and knowledge of the process and operations to be performed in the area~~
529-531	Comment: Per ISO 14644, classification can only be performed in the 'at rest' or static condition Proposed Changes: "In operation" monitoring, ~~classification, qualification and requalification~~ may be performed during normal operations, simulated operations or during aseptic process simulations (where worst case simulation is required).
537-538	Comment: The content provided is consistent with the comment made at line 505 where it was stated that meeting ISO 5 'in operation' requires a design that performs to a higher class in the 'at rest condition'. Proposed Change: Relocate this comment to the vicinity of Line 505 and adjust Table 1 accordingly.
544	Comment: This Table lacks the personnel monitoring levels that are in Table 6. Make them identical and consider whether both are needed, and if only one Table is kept where it should be located.
550-551	Comment: This statement is particularly inappropriate for this document, which consistently misinterprets the distinction between classification and monitoring. This guidance should heed its own advice. There is no statistical or analytical difference between 0 cfu and 1cfu. Zero (0) cfu in microbiology does not mean viable organisms aren't present and does not mean sterile conditions exist. Zero only means nothing grew. Growth-based methods cannot discriminate at levels like zero or one cfu, therefore requiring an investigation at 1 cfu is wrong headed and scientifically a complete waste of time and resources Proposed Change: (b) It should be noted that for grade A the expected result should be 0 cfu recovered; ~~any recovery of 1 cfu or greater should result in an investigation.~~
555-556	Comment: This document should heed the statement made here. The document blurs the distinction between classification ('at rest' state) and monitoring ('in operation' state). The document needs to make the difference clear and avoid the confusion it creates when it suggests, as it does repeatedly, that any environment can be 'classified' while in normal or simulated operation. The changes needed are extensive and not detailed here.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
571-572	Comment: The use of more than one disinfecting agent in conjunction with a sporicidal agent is not good practice. A single disinfectant used with a single sporicide in an uneven rotation is sufficient to control microbial populations. Proposed Change: ~~More than one type of~~ A single disinfecting agent ~~should be employed,~~ with ~~and should include the~~ periodic use of a sporicidal agent should be employed to maintain control over microbial populations.
575-577	Comment: There is no documented evidence to support the development of resistance to disinfectants. The occasional presence of spores in aseptic environments should be recognized as a normal situation. Proposed Changes: Monitoring should be undertaken regularly in order ~~to show the effectiveness of~~ check the general hygiene of the facility as provided by the disinfection program ~~and to detect the development of resistant and/or spore forming strains~~.
588-589	Comment: The mention of any specific technology should be avoided. Proposed Changes: Fumigation or vapour disinfection of clean areas ~~such as Vapour Hydrogen Peroxide (VHP)~~ may be useful for reducing microbiological contamination in inaccessible places.
607	Comment: Areas are not ordinary sterilized. Proposed Changes: … the area should be cleaned, and disinfected ~~and/or sterilized~~ where appropriate …
616-617	Comment: Revise for greater clarity. Proposed Change: Minimizes ~~Prevents~~ chemical, microbial and particulate contamination of the equipment ~~product during the process and prior to disinfection~~.
672	Comment: The production of WFI from Purified Water should not be required. WFI can be produced from supply water that need not meet the Purified Water specifications. Proposed Change: Water for injections (WFI) should be produced ~~from purified water~~, stored and distributed …
688-689	Comment: The use of hydrophobic bacterial retentive vent filters on WFI storage tanks is a poor design. WFI is not a sterile material and such filters serve no purpose. Proposed Change: ~~7.12 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters the filters should be sterilized, and the integrity of the filter tested before and after use.~~
715-716	Comment: The production of pure steam from Purified Water should not be required. Proposed Change: ~~Purified~~ A consistent water supply, meeting the input specifications ~~with a low level of endotoxin~~, should be used as the minimum quality feed water for the pure steam generator.
723	Comment: There are no defined limits for steam condensate quality for pure steam. Proposed Change: … superheat ~~and steam condensate quality.~~
751-752	Comment: There are no defined means for the sterilization of vacuum and cooling systems that are readily adaptable to existing equipment where that was not a consideration upon installation. Proposed Change: ~~There should be periodic cleaning/disinfection of both the vacuum system and cooling systems.~~

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
770-772	Comment: The cautionary content differs from that provided at lines 760-763 and adds additional concerns lacking sufficient clarity. Revise for greater consistency and clarity. Proposed Change….because the product actively supports microbial growth and/or must be held for a long periods before sterilisation and/or is not processed mainly in closed vesselsthe filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, or the product is held for extended periods prior to terminal sterilization
802-803	Comment: Absolute prohibitions on materials liable to generate fibres preclude the use of all common gowning materials. Proposed Change: Materials liable to generate fibres should not be permitted in clean areas.
805-809	Comment: By themselves separative technologies do not alter the need for interventions of any type which will still be required to execute the aseptic process. Properly designed and implemented separative technologies (ISO 14644-7) can mitigate the risk associated with the execution of interventional activities. Automation and robotics reduce the need for human interventions. Proposed Changes: Where possible, the use of equipment such as RABS, isolators or closed systems, should be considered in order to reduce the need for interventions into the grade A environment and minimize the risk of contamination. Robotics and Automation automation of processes can should also be considered to eliminate human remove the risk of contamination by interventions (e.g. dry heat tunnel, automated lyophilizer loading, SIP).
815	Comment: An aseptic connection occurs when sterile surfaces are exposed to the environment. That does not happen when a steam-in-place connection is properly used. See lines 832-834. Proposed Change: Grade A ISO 5 - Aseptic connections (should beexcept where they are sterilized by steam-in-place whenever feasible).
815	Comment: Staging and conveying of sterile primary packaging components within sealed containers could be construed not to conform with this requirement. Revise for greater clarity. Proposed Change: Staging and conveying of sterile primary packaging components (components in hermetically sealed containers are excluded from this requirement).
815	Comment: Control over contamination is improved when cleaned items are protected by unidirectional air during wrapping prior to sterilization. Proposed Change: Grade D ISO 8 – Handling, assembly and wrapping of components, equipment and accessories after washing and prior to sterilization should be performed under unidirectional air flow. Assembly of cleaned equipment to be sterilized.
817-819	Comment: This content is redundant with that provided earlier. Additionally no comparable content is provided for RABS systems. Proposed Change: Note: If Isolators are used then a risk assessment should determine the necessary background environment grade; at least a minimum of grade D should be used. Refer clauses 5.19-5.20.
821-823	Comment: This guidance is improperly stated as it would only apply to equipment used in these processes after sterilization. Proposed Change: Where the product is not subsequently sterile filtered, the unwrapping, assembly and preparation of sterilized equipment, components and ancillary items and products should be done in a grade AISO5 environment with a grade BISO 6 background.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
839-843	Comment: The stated requirement support the use of robotics or other automation in only this instance while their utility in eliminating manual activities potentially much wider. Relocation of this recommendation is more appropriate at lines 825-828 where it would apply more broadly to aseptic processing in general. This specific recommendation if retained should be relocated after line 1850. Proposed Change: … at all times ~~and, where possible, without operator intervention~~.
847-848	Comment: The recommendations can be misinterpreted and potentially restrictive. Cleaning might be best accomplished disassembled, followed by reassembly and sterilization-in-place. Revise for greater clarity and flexibility of processing. As reworded equipment cleaning could be performed either disassembled or in-place. Proposed Change: Whenever feasible, product contact piping and equipment should be ~~pre-assembled, then cleaned and~~ sterilized in place.
852-853	Comment: Time limits for these activities are substantially more important in other than isolator installations. That needs to be added to the document. Proposed Addition at line 874: The use of isolation technology typically allows for longer holding times for items / activities kept within the Grade A environment as compared to RABS or conventional cleanrooms.
877-881	Comment: Revise for greater clarity and flexibility. Proposed Change: ~~Partially stoppered vials or prefilled syringes~~Open containers should be maintained under grade A conditions (e.g. use of isolator technology, grade A with B background, with physical segregation from operators) or grade A ~~LAF~~ UAF carts (with suitable grade B background environment and physical segregation from operators) at all times until the container is closed ~~stopper is fully inserted~~.
883-886	Comment: Requirements for 100% container closure integrity testing mandates testing of quality into the product. It also implies that the closure methods for containers cannot be adequately validated by appropriate means. The first sentence in this paragraph is sufficient. Proposed Change: ~~Containers closed by fusion, e.g. Form-Fill-Seal Small Volume Parenteral (SVP) & Large Volume Parenteral (LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing.~~
905, 909	Comment: Elimination of a confusing statement inserted during the last revision of Annex 1. Proposed Change: … by unidirectional air ~~grade A supply~~ …
919-920	Comment: RABS and isolators do not reduce the incidence rate of human interventions; they reduce the contamination risk associated with the execution of interventions. Separative technologies provide better contamination control by making direct intervention impossible. Revise for greater clarity. Proposed Change: RABS and isolators may be beneficial in assuring the required conditions and minimising the contamination risks associated with direct human interventions into the capping operation.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
931-932	Comment: Inspection of containers for defects is not an absolute process even if automated. The potential for a defective unit to be accepted is always present. Proposed Change: Critical defects should not be identified during any subsequent sampling of acceptable containers as it indicates a possible failure of the original inspection process.
946	Comment: Reconfirmation of the automated inspection equipment performance with a calibrated set of defects (the usual practice across the industry) should only be performed before and after the product inspection to minimize potential mix-up that might occur if it were performed at intervals during the inspection process. Proposed Change: … and the performance of the equipment checked prior to ~~start up~~ and at after product inspection~~regular intervals~~.
955-960	Comment: This sentence adds no value to the document. The included and correct definition of terminal sterilization embraces a wide range of processes when it is understood that the target of the sterilization process is the bioburden present and not the biological indicator (see USP <1229>). Sterilization processes are intended to DESTROY the bioburden present (and opposed to reduce its population) and thus the conditions necessary can be less rigorous than those previously utilized which are fixated on killing high populations of a resistant biological indicator. The false expectation that mandates biological indicator destruction reduces the use of terminal sterilization rather than increasing it. Reduction of biological indicator population actually supports extremely safe terminal processes for the substantially less resistant bioburden which will be completely destroyed. Proposed Change: Delete the last sentence in this section. ~~Where it is not possible for a product to undergo a sterilization, consideration should be given to using terminal bioburden reduction steps, such as heat treatments (pasteurization), combined with aseptic processing to give improved sterility assurance.~~
970-973	Comment: The text adds unnecessary prohibitions which may serve to reduce the use of terminal sterilization rather an expand it. This is contrary to expectations for improved patient safety through the wider use of terminal sterilization. It also serves as an impediment to innovation. Proposed Change: ~~Particular attention should be given when the adopted sterilization method is not described in the current edition of the Pharmacopoeia, or when it is used for a product which is not a simple aqueous solution.~~
977-980	Comment: Sterilization cycle development and validation for all processes other than radiation sterilization requires both physical and microbiological evidence. Proposed Change: Before any sterilization process is adopted, its suitability for the product and equipment and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators ~~where appropriate~~.
997	Comment: Greater clarity is required in addressing the 'quality' of biological indicators. See USP <1229>. Proposed Change: … the population and identity ~~quality~~ of the batch/lot should be …

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1053-1055	Comment: There is no evidence that any particular endotoxin represents a 'worst case' with respect to its destruction / removal. An arbitrary 3- log reduction requirement using an individual endotoxin type does not provide assurance of removal destruction of other endotoxins (see USP <1228>). Proposed Change: When a depyrogenation process is used for any components or product contact equipment, validation studies should be performed to demonstrate that the process will result in materials that have had their ~~a minimum 3 log reduction in~~ endotoxin content reduced to a safe level.
1063-1064	Comment: There are two reasons that dry heat sterilization is slower than moist heat. The absence of heat of condensation is one; the other reason, unstated in this guidance, is the limited heat capacity of air. Conduction is not a significant factor as that is unchanged as it relates to heat transfer within the load items and not the transfer of heat from the sterilizing medium. Proposed Change: The ~~reduced level of moisture~~absence of heat from condensation of steam and the limited heat capacity of air in dry heat sterilization process reduce heat penetration ~~which is primarily effected by conduction~~.
1086-1087	Comment: Physical measurements rely upon mathematical models from microbiological data which estimate the lethal effect a process asserts on microorganisms. As such physical measurements are substantially less reliable (though easier to acquire) than the biological results they attempt to mimic. They should never be given preference over the results of a microbiological challenge study. Additionally, there are locations within items requiring sterilization where physical measurements are taken so remotely that their ability to 'demonstrate' lethality is either extremely limited or non-existent. The limitations of chemical indicators were stated previously at Lines 1005-1012. Proposed Change: The results from ~~Chemical or~~ biological indicators ~~may also be used, but should not take the place of~~ and physical measurements must be considered in validation activities.
1089-1091	Comment: This requirement is arbitrary and while well intended it may be problematic especially in terminal sterilization where it may extend the cycle dwell with potentially adverse effects to those items receiving the most time-temperature. It may have no utility at all in actual practice. If retained in the document its non-applicability to terminal sterilization needs to be stated. It should be understood, that the 'required' temperature stated herein is generally not the set point for the sterilizer dwell period. The content as written has the potential for over-processing of materials with a deleterious impact on them. Proposed Change: ~~Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time period is commenced. This time must be determined for each type of load to be processed.~~
1093-1096	Comment: The last sentence in this paragraph is specific to terminal sterilization (discussed previously at Lines 756-784) and should be relocated to that section. Proposed Change: After the high temperature (dwell) phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling ~~fluid~~ liquid or gas in contact with the ~~product~~ load should be sterilized. ~~unless it can be shown that any leaking container would not be approved for use.~~
1098	Comment: Discussion of terminal sterilization and porous load sterilization should be separated for greater clarity. Integration of content for these different processes in a single document has the potential to cause confusion. See USP <1229.1> and <1229.2> as an example of this treatment.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1121-1124	Comment: The stated requirement is excessive where no vacuum is used in the sterilization cycle. The frequency should be determined by QRM, and not mandated as 'frequent' without that assessment. Proposed Change: There should be ~~frequent~~ leak tests on the system to be sterilized when a vacuum phase is part of the cycle or the system is returned, post-sterilization, to a pressure ~~equivalent to or~~ lower than the environment surrounding the sterilized system. The frequency of testing should be based on the principles of QRM.
1126	Comment: Poor choice of words and wording adds potential confusion. Proposed Change: ~~When the sterilization process includes air purging (e.g. porous autoclave loads, lyophilizer chambers)~~ there should be adequate assurance of air removal prior to and during sterilization when the sterilization process includes air removal (e.g. porous autoclave loads, lyophilizer chambers).
1131-1133	Comment: Omitted content regarding the need to remove condensate from load items. Proposed Change: The items to be sterilized, other than products in sealed containers, should be dry, wrapped in a material which allows removal of air / condensate and penetration of steam but which prevents recontamination after sterilization.
1136-1138	Comment: The content requires expansion as damage to containers extends to other container configurations. In addition, the heating /cooling rates used can cause similar issues. Clarification of terminology as well. Proposed Changes: Distortion and damage to ~~of flexible~~ containers~~, such as containers produced by Blow- Fill-Seal and Form- Fill-Seal technology~~ that are terminally sterilized~~,~~ should be prevented by setting correct ~~counter~~ air over-pressure, heating and cooling rates and loading patterns.
1140-1143	Comment: This content was previously included at Lines 1093-1096. Proposed Changes: ~~Care should be taken to ensure that materials or equipment are not contaminated after the sterilization exposure phase of the cycle due to the introduction of non-sterile air into the chamber during subsequent phases; typically only sterile filtered air would be introduced into the chamber during these phases.~~
1151-1153	Comment: Recommendation for improved certainty in the maintenance of sterility. Proposed Change: Once a system has been sterilized by SIP it should remain under positive pressure ~~integral~~ prior to use, the maximum duration of the hold time should be qualified.
1166-1167	Comment: HEPA filter integrity tests as performed with volatile organic compounds for room systems are inappropriate for dry heat systems. Proposed Change: … periodic confirmation ~~of Grade A~~ appropriate total particulate air quality conditions within the tunnel ~~tests~~ should be performed ~~to demonstrate filter integrity~~.
1177	Comment: The uniformity of heat distribution in a dry heat tunnel is not defined given the quite normal and significant variations across the tunnels length and width. Implying uniformity would result in firms imposing arbitrary limits serving no useful purpose. Additionally, the very high temperatures utilized in tunnels (typically >275C) are such that the risk associated with temperature variation in this process is low. Proposed Change: Heat distribution~~/uniformity~~

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1179	Comment: Airflow velocities in dry heat tunnels are not important to the successful sterilization / depyrogenation of materials. The relevant concern is that the tunnel discharge be maintained at a higher static pressure than the tunnel inlet and this was stated in lines 1162-1165. Note that no similar requirement has been stated for the dry heat ovens, nor should there be for either piece of equipment. NOTE: Because air is such a poor conductor of heat, uniformity of temperature across an oven is actually better when there is more air (higher velocity) supplied to the colder locations (typically lower in the oven). Proposed Change: ~~Airflows – correlated with the heat distribution and penetration studies~~.
1187	Comment: Air circulation should be maintained with dry heat ovens from cycle start through removal of the items from it. Proposed Change: They should be maintained at a positive pressure to lower grade areas throughout the process cycle and until unloaded.
1220	Comment: There are other sterilizing gases proven effective for sterilization. While specific guidance on their use is not necessary some mention that alternative gases can be used for sterilization should be added. The content in this section requires minimal modification to make it applicable to other gases. One note of caution: hydrogen peroxide and other vapour agents delivered as heated gases are subject to condensation upon cooling and MUST NOT be considered in the same content as true gases that will never condense under the conditions used for sterilization.
1281	Comment: This bullet point suggests that filters and their housings can be cleaned in the same manner as the remainder of the process train. There are no valid methods for cleaning of sterilizing filters and filter housings in situ. Proposed Change: ~~Allow cleaning procedures to be conducted as necessary.~~ Sterilizing filters are single use, and filter housing shall be removable for cleaning.
1287-1289	Comment: Pre-use post-sterilization integrity tests of sterilizing filters should only be performed where a closed system is present throughout. Requiring PUPSIT where the system is not closed creates a greater risk than any value the integrity test can provide. This same expectation is repeated at lines 1331-1340. At the very least, content on the same subject should be together in the document. Proposed Change: ~~Permit in-place integrity testing, preferably as a closed system, prior to filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.~~
1331-1334	Comment: See the previous comment. Proposed Change: The integrity of the ~~sterilized~~ filter assembly should be verified ~~by testing before use~~, in case of damage and loss of integrity caused by processing~~, and should be verified~~ by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test.
1346-1347	Comment: The use of hydrophobic filters has nothing to do with the moistening or wetting of filters which is independent of the type of filter installed. The concern is relevant, but unrelated to the type of filter used. Proposed Change: For gas filtration, the avoidance of unintended moistening or wetting of the filter or filter equipment is important. ~~This can be achieved by the use of hydrophobic filters.~~

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1349-1352	Comment: See comment for lines 1287-1289. Repeating the same requirement over and over again makes it no more useful than a single statement. Proposed Change: Where serial filtration (one filtration is followed by a subsequent filtration) is a process requirement the filter train is considered to be a sterilizing unit and all sterilizing-grade filters within it should satisfactorily pass integrity testing ~~both before use~~, in case of damage during processing~~, and~~ after use.
1360	Comment: Clarify the use of a single filter for campaign production. Proposed Change: … of a single lot / campaign.
1366-1368	Comment: The organization of the document can be improved by a minor edit. Proposed Change: Form-Fill-Seal (FFS) units include ~~blow moulding from thermoplastic granulate and~~ thermoforming from thermoplastic film ~~typically~~ known as ~~Blow- Fill-Seal (BFS) and~~ Vertical-Form-Fill-Seal (VFFS) respectively.
1372-1373	Comment: Confirmation of container-closure integrity is expected for all product configurations and is confirmed through validation of the operational controls. Mandating 100% integrity testing is nothing more than testing quality into the product. The appropriate controls are identified in the next paragraph. Proposed Change: ~~All such containers are considered to be sealed by fusion and, as such, fall under the requirement to perform 100% integrity testing.~~
1375	Comment: Appropriate content paralleling that in section 8.94 (lines 1392-1448) for BFS should be inserted for FFS.
1492	Comment: The document could be improved by a more comprehensive definition of closed systems. Preferably brief at this point, and more detailed in the glossary. PDA TR#28 revision includes content that would assist in the definition.
1494-1495	Comment: Isolators are closed systems as they conform to the design elements outlined in PDA TR # 28 revision. They should be included in this opening section. Proposed Change: Closed systems can be ~~both~~ single use systems (SUS) (i.e. disposable), isolators (open and closed) and fixed systems (such as vessels with fixed pipework).
1498-1499	Comment: Closed systems are unaffected by interventions which are irrelevant because of the closed system design. They are superior to open systems because of the totality of separation provided between sterile materials and potentially contaminating factors such as personnel or background environment. It's not about the interventions, it's about the physical separation between personnel and sterile materials when using closed systems. Proposed Change: The use of closed systems can reduce the risk of both microbial and chemical contamination due to ~~interventions~~ the completeness of separation provided between sterile materials and potential contaminants~~contaminating factors~~.
1517	Comment: Since many single use systems of critical importance are also closed systems, this section should become a subcomponent of the preceding section on closed systems. Single use systems that are not closed, typically filling set-up systems, are closed until just prior to their use and thus the content applies. Particularly useful is the content in section 8.118 as it also relates to closed systems that are also single use disposable.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1522, 1532	Comment: Single use systems should always be designed to reduce rather increase both the need for, and complexity of manual interventions. Proposed Change: Insert at line 1522 where it is most appropriate. Single use systems should always be designed to reduce rather than increase both the need for, and complexity of manual interventions. Delete the content at Line 1532 ~~Increase in number and complexity of manual operations and connections made.~~
1538-1540	Comment: These considerations are essentially the same. Proposed Change: ~~Pin-hole and leakage.~~
1549	Comment: Many single use systems are sterilized prior to use and it must be shown that process is effective, and has no deleterious impact on system performance. Proposed Change: Add the following k) Sterilization processes for single use systems must be validated and shown to have no adverse impact on system performance.
1584-1586	Comment: Environmental and process monitoring is a low resolution and untimely assessment system which does not provide a direct means for the mitigation or control over contamination risk. Proposed Change: The site's environmental and process monitoring program forms part of the overall contamination control strategy ~~designed to minimise the risk of microbial and particulate contamination.~~
1615-1619	Comment: The only relevant information collected by the environmental monitoring program is that which relates to the conditions when the system is in the operational state, and not when it is in disrepair or contaminated. There should be a defined process for restoring a controlled environment from non-operation to full operating condition. Proposed Change: Monitoring should also be performed outside of operations within the area, e.g. ~~pre disinfection,~~ post disinfection, prior to start of manufacturing ~~and after a shutdown period~~, etc., in order to detect potential incidents of contamination which may affect the controls within the areas. Collection of environmental results in the non-operational state may be useful in establishing decontamination practices. The number of samples and frequency of monitoring should be considered ~~-~~ based on operational experience. In ISO 5 environments where the contamination recovery rate is extremely low consideration can be safely given to reduced monitoring intensity.~~in the context of the risk assessments and contamination control strategy.~~
1629	Comment: There are no appropriate means to distinguish the low levels of microorganisms typically detectable with Grade B environments necessary to establish alert levels. Microbiological monitoring of air and surfaces with low population is not possible. Proposed Change: The alert limits for grade ~~B,~~ C and D should be set based on the area …
1651	Comment: For consistency between Tables 1 and 5, the 'at rest' columns should precede the 'in operation' columns in Table 5.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1659	Comment: The inability to accurately count low numbers of non-viable particles with current technology precludes the imposition of limits for 5 µm particles in ISO 5. This objection has been raised innumerable times by numerous individuals and organizations since the first issue of Annex 1 in 1999. Maintaining the façade that this is a statistically meaningful measurement is inappropriate as it perpetuates a technical fallacy. There is no scientific justification for retaining a monitoring requirement for 5 µm particles in this guidance. Proposed Change: Delete the columns relating to 5 µm particles in Table 5 and Note 2. ~~Note 2: With regards to the monitoring of 5.0 µm, the limit of 20 is selected due to the limitations of monitoring equipment. It should be noted that alert limits should also be set based on historical and qualification data, such that frequent sustained recoveries below the action limit should also trigger an investigation~~.
1703-1705	Comment: See the preceding comment. Further, the suggestion that larger particles would serve as a superior 'important diagnostic tool' than smaller particles, which are more accurately counted is not supported by documented evidence. Persistence in including this 'requirement' in the face of objective scientific evidence to the contrary is completely without justification. Proposed Change: ~~Although monitoring of ≧ 5.0 µm particles are not required for room qualification and classification purposes, it is required for routine monitoring purposes as they are an important diagnostic tool for early detection of machine, equipment and HVAC failure.~~
1707-1712	Comment: See the two previous comments. Proposed Change: ~~The occasional indication of macro particle counts, especially ≧ 5.0 µm, may be considered false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration (HVAC) system, filling equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation~~.
1725-1726	Comment: Monitoring of personnel during the conduct of aseptic operations is an interventional activity that adds risk to all subsequent activities performed by those personnel. This is contrary to the objectives of minimizing activity in aseptic operations. This is mandating an increase in interventional activity in proximity to sterile materials, an extremely poor practice that should never be considered. Additionally there is greater potential for contamination of the operator as a consequence of the added monitoring. See section 9.29 of this guidance. Proposed Change: Particular consideration should be given to monitoring personnel ~~following involvement in critical interventions and~~ on exit from the ~~grade A/B~~ aseptic processing area.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1728-1733	Comment: There is no definition of 'continuous monitoring' provided and to the extent that the expectation for it is satisfied by passive monitoring in the form of settle plates there is no difficulty. Although, the use of settle plates as well as active air sampling is unjustified since these sampling approaches measure the same thing. Firms should be allowed to utilize one or the other rather than both, particularly in ISO 5 environments where the recovery of contamination is a rare event regardless of the sampling method. If the expectation is for active air sampling, the required use of both methods redundantly to evaluate air has the impact of adding risky interventional activities in proximity to sterile materials for no added value. No amount of environmental monitoring can confirm sterility, which is of course unobtainable in aseptic processing. There are no means to eliminate risk in relation to this monitoring expectation. Proposed Change: ~~The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations is avoided.~~ Add to the glossary ~~–~~ Continuous Monitoring - monitoring using settle plates is an accepted means of satisfying that requirement.
1747	Comment: The location where personnel working in ISO 5 are to be sampled to comply with the Table 6 requirements is not specified. In order to best protect the materials being produced that sampling should be performed in ISO 6. Expand Table 2 and refer to it instead of using nearly the same table in two different places. Proposed Change: Add a note below Table 6. Note: Monitoring of personnel who have worked in ISO 5 should be performed in the surrounding background environment (ISO 6). Personnel working exclusively in ISO 6 shall be sampled in ISO 6.
1753-1754	Comment: The objective target of 0 CFU reflects the low probability of microbial recovery in ISO 5 environments. However, the target should be given as 'not recovered' not zero cfu. No growth on a plate does not confirm or even imply sterility; it only means no contamination was recovered. The realities of aseptic cleanroom operations in ISO 5 and ISO 6 are such that microorganisms will occasionally, but infrequently be recovered. Modern aseptic clean rooms routinely operate at levels below the limit of detection of EM sampling methods. Investigations into such recoveries are rarely fruitful, wasteful of resources and generally inconclusive. Proposed Change: (b) It should be noted that for ~~grade A~~ ISO 5 the expected result should be ~~0 cfu~~ 'not recovered;' the typical result will be zero because monitoring in such rooms is unlikely to be capable of recovering contamination. ~~any recovery of 1 cfu or greater should result in an investigation.~~

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
1796-1797	Comment: There is substantial confusion regarding what the authors actually mean when they write 'anaerobic conditions'. The inclusion of a specific value would clarify the requirement substantially. The use of nitrogen to reduce the oxygen content in the headspace of the container does not result in the attainment of full anaerobic conditions. Technically anaerobic conditions are those in which the level of O_2 is below the limit of detection. Oxygen is toxic for strict anaerobes and therefore their existence as a risk factor in the vast majority of aseptic processes is impossible. Even where inert gas headspace is required for product stability up to 2% residual O_2 levels may exist. The extent to which microbiological testing is required, if at all, can best be determined by HACCP evaluation. Proposed Changes: Aseptic manufacturing performed in a strict anaerobic environment may require evaluation for micro-aerophilic organisms. The need to do specific testing for such organisms can be determined by a HACCP evaluation~~should be evaluated with an anaerobic media in addition to aerobic evaluation.~~
1808-1810	Comment: The contamination risks associated with lyophilization relate primarily to the loading / unloading of the chamber and the drawing and breaking of vacuum. The guidance is unclear as to the duration of the simulation in the lyophilizer chamber. Mandating that lyophilization simulations extend for the full duration of the process cycle is inconsistent with industry norms and of no significant risk management value for most processes. A HACCP evaluation may be done to determine if specific controls are required. Proposed Changes: The process simulation should duplicate the lyophilization process, with the exception of freezing and sublimation, including partial vacuum and abbreviated cycle duration and parameters as appropriate for the media. If a review of the process indicates a reason for contamination control concern, the need for or nature of such controls can best be determined by HACCP evaluation.
1958-1964	Comment: Paragraph 10.2 conflicts directly with paragraph 10.3. Are terminally sterilized batches to be subjected to bioburden analysis on an every-batch basis or not? The evaluation on a lot to lot basis should not be necessary for processes that are well-validated for control by means of a suitable risk management system such as HACCP.
1974-1975	Comment: Edited for greater clarity. Proposed Change: The sterility test should be performed under aseptic conditions, which are at ~~least consistent with~~ ~~the standard of clean room required~~ comparable to those used for the aseptic manufacture of ~~pharmaceutical~~ sterile medicinal products.
1982-1986	Comment: This section wrongly implies that sterility testing is capable of reliably detecting contamination despite the severe statistical limitations it possesses. In reality sterility testing can only find comparatively heavily contaminated product. Testing quality into the product in this manner is ludicrous. Proposed Change: ~~a) Products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention.~~ ~~b) Products which have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.~~

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
2037-2038	Comment: The offered definition of asepsis overstates the reality. Moreover it includes circular reasoning. Asepsis means free of potential infectious organisms it does not mean sterile. Sterility and asepsis are not the same thing and should never be equated. Proposed Change: Asepsis - A state of control attained by the establishment of appropriate deigns and controls that minimize the potential for ~~using an aseptic work area and performing activities in a manner that precludes~~ microbiological contamination of the exposed sterile medicinal product.
2048-2049	Comment: This definition is appropriate for RABS, but not for isolators which are substantially more effective in separation of environments. Isolators are also subject to leak testing and automated decontamination which RABS and barrier systems cannot be. Proposed Change: Barrier - A physical partition that affords aseptic processing area (grade A) protection by partially separating it from the surrounding area such as RABS ~~or isolators~~.
2054-2055	Comment: The last sentence in the definition includes an error. Proposed Change: Incoming lot D-value and microbiological count within a reasonable allowance of +/- 0.5 log and purity define ~~the quality of~~ the BI.
2057-2068	Comment: The definition includes content found in the body of the document and provides no added guidance. Proposed Change: Blow-Fill-Seal - Blow-Fill-Seal (BFS) technology is a pharmaceutical filling process in which containers are formed from a thermoplastic granulate, filled with product, and then sealed in a continuous, integrated, automatic operation. The two most common types of BFS machines are the Shuttling machine (with Parison cut) and the Rotary machine (Closed Parison) types. ~~The equipment design, operation, and therefore controls for these differ. For Shuttling systems the processes of container extrusion and filling occur at two separate locations within the machine. The extrusion of the container parison occurs adjacent to the filling zone, the extruded plastic is collected from underneath the extruder head, is cut and formed and automatically transferred (usually by horizontal shuttling) to the filling and sealing zone. For Rotary design machines the filling needles are enclosed within the extruded parison and therefore there is limited exposure of the inner surfaces of the container to the external environment.~~
2076-2084	Comment: This definition on CNC far exceeds current industry practices. In many facilities the CNC area is nothing more than corridors and hallways. Proposed Change: Clean Non Classified (CNC) area - An area that does not meet any of the formal pre-determined ~~grades~~ classification ~~of cleanliness included in the Annex, i.e. grades A to D,~~ but where a manufacturer defined level of microbial and particle control ~~is still~~may be appropriate~~required~~. The area ~~should~~ may be subject to a formal cleaning/disinfection regime and formal environmental monitoring program to achieve the defined level of control. The level, type and frequency of both the cleaning program and the environmental monitoring program (including contamination limits) should be based on a formal risk assessment (captured within the wider contamination control strategy) and should be commensurate with the specific risks to the ~~processes and product performed manufactured~~activities within each CNC area.
2091-2092	Comment: This definition is inadequate for closed systems which are increasingly important in sterile product manufacture. Proposed Change: Draw upon the more detailed information on closed systems as provided in PDA TR #28 revised.

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2128-2129	Comment: Confuses classification with monitoring. Proposed Change: Dynamic - Conditions relating to clean area ~~classification~~ monitoring of ~~under~~ normal production operations.
2114-2115	Comment: The definition of D-value should be modified to provide for application in sterilization processes that are non-thermal and for consistency with other sterilization standards. Proposed Change: The time ~~(in minutes)~~ of sterilization process exposure at specified lethal conditions ~~given temperature~~ that causes a one-log or 90 per cent reduction in the population of a pure strain of ~~specific~~ microorganism.
2128-2129	Comment: Classification under dynamic conditions is a misnomer. Sampling under dynamic condition is monitoring. Clean rooms cannot be classified microbiologically under either static or dynamic conditions. Proposed Change: Dynamic - Conditions relating to clean areas ~~classification~~ under normal production operations.
2149	Comment: HEPA filters are available with various particle capture efficiencies. This definition is specific to a particular rating of HEPA filters Proposed Change: HEPA filter (H13) - High efficiency particulate air filter with minimum 0.3 µm particle retaining efficiency of 99.97 percent.
2201-2203	Comment: This definition of qualification goes beyond conventional practice. In mimicking a definition of validation it suggests that equipment can be 'validated'. Processes and products can be 'validated', however equipment used for that purpose is 'qualified'. Proposed Change: ~~Qualification - Establishing documented evidence that provides a high degree of assurance that equipment or facilities will perform to the required specification detailed in the user requirement specification and the design qualification.~~ Qualification – A continuing program which establishes that facilities, equipment, and utility systems are properly installed, operated and maintained.
2205-2215	Comment: The most important distinction in RABS design and operation is omitted, while less significant concerns are included. Proposed Change: Restricted Access Barrier System (RABS) - A restricted access barrier system (RABS) provides an enclosed, but not closed, environment meeting defined cleanroom conditions using a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment. ~~Active RABS: integral HEPA-filtered air supply~~ ~~Passive RABS: air supply by ceiling mounted HEPA-filters.~~ Open RABS. A RABS design where occasional opening of the enclosure is required during the process to allow for operator access to ~~Where there are vents in the barrier that allow air to move from~~ the grade A areas from ~~to~~ the grade B area. Closed RABS: A RABS design where opening of the enclosure is not required during the process. All access is accomplished by material transfer via aseptic connections.

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2225-2227	Comment: Includes an extra word which adds confusion to the definition. Proposed Change: Single Use Systems (SUS) - Systems in which ~~some~~ product contact components are used only once (i.e. single use components) to replace reusable equipment such as stainless steel transfer lines or bulk containers.
2232-2235	Comment: The definition is incomplete. It also uses SAL rather than PNSU which is substantially easier to interpret. Proposed Change: Terminal sterilization - The application of a lethal sterilizing agent to finished product within a sealed container to achieve a predetermined Probability of a Non-Sterile Unit ~~sterility assurance level~~ (PNSU~~SAL~~) of 10^{-6} or better (i.e. the theoretical probability of there being a single viable microorganism present on or in a sterilized unit is equal to or less than 1 x 10-6 (one in a million)). The estimation of the PNSU is based upon the population and resistance of the bioburden present in the container.
2237	Comment: ULPA's have no practical value in manned or unmanned aseptic processing. Proposed Change: Delete this definition and any mention of ULPA's in the entire document.