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March 20, 2018

Directorate-General for Health and Food Safety (EC)
Unit SANTE B/4
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SANTE-REVISION-ANNEX-1@ec.europa.eu

Reference: Annex 1: Manufacture of Sterile Medicinal Products

Dear EC/EMA:

PDA appreciates the opportunity to respond to the proposed revision of Annex 1. We welcome the revision and acknowledge the tremendous effort to revise the Annex to integrate new concepts and to facilitate introduction and implementation of innovative technologies, therefore paving the way of the regulatory framework for the next decades of sterile product manufacture.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing and pharmacopeia publications including members representing our Board of Directors and our Science Advisory Board.

This revision addresses a wide range of complex topics with some excellent and much needed improvements. PDA especially is pleased to see and supports the clarification of aseptic process simulation acceptance criteria of zero contaminated units. This is a practice that illustrates the objective of modern, well designed, risk based aseptic processes. PDA also is pleased and supports the risk-based approach to the selection of media incubation duration and temperature, justified and appropriate for the process being monitored, the growth medium, and targeted contamination.

The PDA has identified areas where, because of the complexity of the subject matter and varying experience of companies, there may be the potential for misinterpretation that may result in quality and compliance risk. Therefore, the clarity of text and intent are essential to the best understanding of the principles presented. The replacement of certain technical terms throughout the Annex will enhance clarity and promote risk-based thinking.

PDA is pleased to see the emphasis on risk-based thinking and decision making throughout the revision. However, more explanation of expectations and guidance would help those tasked with making process control related decisions to avoid the misuse or ineffective use of risk-based approaches.

Regarding the reduction of risk, two topics are of particular note. The first is required use of post sterilization, pre- use filter integrity testing (AKA PUPSIT), as





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the primary means to reduce the risk of filter failure. The second is the requirement for the placement of settling plates in grade A critical areas.

We feel that the revision is an opportunity to promote a more scientifically practical understanding of contamination and contamination control strategies. We feel that clarification of intent for such methods as aseptic process simulation, air flow visualization, environmental monitoring, and personnel qualification can point out where these methods are best suited and where their limitations should be realized to avoid misinterpretation of results and a false sense of security. In addition, we believe that the revision of the Annex 1 should reinforce the benefit of and support for the use of aseptic processing systems that limit human access and interventions, including isolators and closed RABS.

PDA's expert committee has provided comments (detailed general and specific along with proposed changes) to further clarify the points made herein, which are in the attached table. We trust that these comments and suggestions will be received in the spirit in which they are presented. If there are any questions, please do not hesitate to contact me.

Sincerely,

A handwritten signature in black ink, appearing to read 'Falk Klar', is written in a cursive style.

Falk Klar

General Manager, Vice President PDA Europe

CC: SANTE-Revision, EC, Simona Keckesova, EMA, Jahanvi (Janie) Miller, PDA

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

Comments from:

Name of organisation or individual

Parenteral Drug Association c/o Janie Miller (miller@pda.org)

1. General comments

PDA General Comments:

PDA welcomes the revised Annex 1 and acknowledges the tremendous effort to revise the GMP annex to integrate new concepts (e.g. quality risk managements) and to facilitate introduction and implementation of innovative technologies, therefore paving the way of the regulatory framework for the next decades of sterile product manufacture.

PDA assembled a team of sterile manufacturing and quality control experts. Using input from PDA members, documented PDA positions from its Technical Reports, Aseptic Processing Points to Consider (2015, 2016), Journal Articles, and the team's acquired knowledge, this team reviewed the Annex 1 Revision, and where necessary offered comments and recommendations on and to the Annex 1 Revision.

In general, this revision addresses a wide range of complex topics with some excellent and much needed improvements. PDA especially is pleased to see and supports the clarification of aseptic process simulation acceptance criteria of zero contaminated units, as noted in section 9.43. This is a practice that illustrates the objective of modern, well designed, risk based aseptic processes. PDA also is pleased and supports the risk based approach presented in section 9.45 suggesting that the selection of incubation duration and temperature should be justified and appropriate for the process being simulated, the selected growth medium, and the targeted contamination.

PDA has identified areas where, because of the complexity of the subject matter and varying experience of companies, there may be the potential for misinterpretation that may result in quality and compliance risk. The clarity of language and intent are essential to the best understanding of the principles presented. Where intent is not fully understood, ambiguity exists that may lead to confusion and lack of appreciation of important recommendations. Please note that in the interest of brevity, the PDA chose to present these general comments, without repeating them at each section where they appear. Where we recommend the use or replacement of a term or word here in the General Comments, we also are recommending its use or replacement throughout the document (whether or not we later note it as a specific comment by line number).

In the interest of clarity, we respectfully offer the following general comments in the table below:

1	Replace the phrase "laminar flow air flow" with "unidirectional air flow". Laminarity according to the glossary refers to an airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight-line vector. This cannot occur in the clean room and would be difficult to show if it did. Instead, the air flow is unidirectional, meaning air cascading in one direction, but not necessarily in a laminar fashion. The intent of the unidirectional airflow is to ensure that the working area, where the sterile product and sterilized components are exposed, is always flushed with clean air, and in general air moves from clean to less clean areas. A requirement for unidirectional air flow will be easier to achieve, demonstrate, and equally valuable for aseptic process control.
2	Replace the phrase "non-viable particulates" with "total particulates". Non-viable particulates may be interpreted as indicating that the particles have no microbiological properties and are therefore not sources of contamination. That, of course, is not always the case. Total particulate more accurately describes what should be monitored and presents a clearer reason and basis for control.
3	Consider harmonizing clean room designation terms grade A/B/C/D and ISO 5/6/7/8. While we are not recommending the use of one air quality term over another, we do feel that it would reduce confusion and redundancy in the industry if global health authorities were harmonized on terms.
4	Provide additional guidance on the use of risk based thinking and decision making. Throughout the document readers are advised to use quality risk management and risk assessment to evaluate information and make process control related decisions. This is welcome; however, these approaches can be better defined to avoid

	<p>misapplication of risk management and lack of understanding. More explanation of your expectations and guidance would help those tasked with making process control related decisions to avoid the misuse or ineffective use of risk based approaches. Further, the use of risk based approaches encouraged in the revision appear to focus on risk identification rather than risk mitigation or reduction. Readers should be reminded that risk reduction is a more effective and cost-effective point of focus, as such a focus would likely result in process improvement and right-first-time deliverables.</p> <p>Regarding the reduction of risk, two topics presented in the Annex are of concern. The first is required use of post sterilization, pre- use filter integrity testing (AKA PUPSIT), as noted in section 8.84 and elsewhere. The use of PUPSIT can add risk and in some instances, it will significantly increase the complexity of the aseptic process, thus increasing the product contamination risk. Readers of the Annex are encouraged to take actions to reduce any additional process risk. Therefore, where other equally effective methods of risk reduction, that do not add PUPSIT related risk, can be applied, those risk reduction steps should be allowed.</p> <p>The second is the encouragement and requirement for the placement of settling plates in grade A critical areas. This requirement may result in decisions not to use certain modern technologies, even though they may reduce overall contamination risk, for which the use of settle plates is not possible/advisable as their use may result in the promotion of potentially risky interventions needed to place and change settling plates in critical areas during critical operations of aseptic filling systems. Therefore, we suggest emphasizing the need for risk assessment and reduction or replacement of the use of this specific method, depending on the risk assessment outcome.</p>
5	<p>Clarify the intent of statements. It is not always clear if the authors intended for a statement to be read as a requirement, a recommendation, a suggestion, or an opinion. Words and phrases such as “encouraged”, “in alignment with”, “typically” or “in consideration of” lack clarity of intent and should be avoided or better defined. Where words such as “should”, “must”, “shall”, “may” and “can” are used, it would be helpful to have a better idea which of these words denotes a requirement, a recommendation, or a suggestion. Qualifying words such as “sufficient”, “appropriate”, “optimized” “similar”, and “suitable”, lack definable criteria and should also be avoided, as they are difficult to objectively define and will likely be different for different companies.</p>
6	<p>Replace “action and alert limits” with “action and alert levels”. The bulk of the document uses the word “limit”, as in “action limits” and “alert limits”. Yet the glossary only defines action and alert levels. We feel that the use “levels” is better than “limits”. Levels denotes an analysis of trends, providing useful information to make informed, sound risk based decisions, as we believe is the overall intent of the revision. Limits denotes an absolute threshold that may never be crossed, not allowing for such risk based decision making. Action and alert levels should be risk based, accounting for cleanroom/process design, technology employed, and historical study results.</p>
7	<p>Promote a more scientifically practical understanding of Contamination & Contamination Control Strategy. While the inclusion of a requirement for a documented contamination control strategy represents a significantly beneficial and powerful means of assuring the manufacture of sterile products, the term “Contamination” appears to be universally applied in the Revision to describe any form of microorganism, particle or pyrogen recovered from, or introduced in to the finished product, raw materials, intermediates, manufacturing processes or environment. It is important for the readers to understand that the introduction of microorganisms, particles or pyrogens in to the finished sterile product, represents product “contamination”, but that the presence of microorganisms, particles or pyrogens in raw materials or the non-critical manufacturing environment does not necessarily represent “contamination”. The consequence, controls, response and implications of “contamination” and bioburden, particles or pyroburden are very different. We are concerned that there may be a misinterpretation of the revision’s intent, in that companies may assume that all microorganisms and microbiological entities represent an equal risk to process quality and product safety and will therefore be given the same priority in the control strategy. If all microorganisms, particulates and pyrogens were to be universally treated as contamination then controls and processes incommensurate with product risk would be established and having no benefit to product safety. We therefore suggest the inclusion of established definitions for Contamination (from ICH Q7A) and Contamination Control Strategy be added to the glossary and that the use of</p>

	Contamination and Contamination Control Strategy (from ICH Q10) in the revision be consistent with those definitions.
8	Recognize the distinction between moist heat sterilization controls needed for porous hard goods loads and liquid loads. As the critical elements regarding the design, development, qualification and ongoing control for the moist heat sterilization of porous hard goods and liquids are vastly different, it is important to differentiate, where necessary, the recommendations and requirements for these two load types. In several cases, recommendations and requirements for moist heat sterilization are positioned broadly in this document to be universally applicable to porous hard goods and liquids while some of these are only relevant for porous hard goods, but not relevant for liquids. Examples include comments provided below to the following Line Number/Sections: Line 715/Section 7.17, Line 1060/Section 8.47, Line 1061/Section 8.47, Line 1089/ Section 8.52, Line 1102/Section 8.54 and Line 1133/Section 8.60.
9	Articulate the limitations of aseptic process simulations (APS). The Annex is an important place to remind readers the purpose and limitation of APS. APS should not be considered as the sole judge of the asepsis of the process. The mere passing the APS does not qualify operators, process steps, procedures, or interventions. This misunderstanding and over-reliance on APS can lead to false sense of security as well as an unnecessary complexity of the simulation exercise. True process confidence should come from proper process and control strategy design, rather than testing.
10	The acronym/term SAL or sterility assurance level in the Terminal sterilization glossary definition (and elsewhere in the revision) should be replaced with the more technically precise and descriptive term: PNSU or probability of a non-sterile unit. Similarly, the mathematical symbol " \leq " should replace the use of the phrase "or better" which is used along with the 10 ⁻⁶ exponent for the Sterility Assurance Level. Example: PNSU \leq 10 ⁻⁶ .
11	This would be a good opportunity to reinforce the benefit of and support for the use of aseptic processing systems that limit human access and interventions, including isolators and closed RABS. Again, these suggestions are meant to be recommendations for clarity. We believe that the authors of this revision had clear intent in mind when they developed it and that intent was to move the industry forward as discussed at so many meetings, workshops, and presentations. Clarity of this purpose and intent can best be achieved with clarity of language.

Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
6-23	<p>Comment: The Scope section states that the Annex provides general guidance that should be used for all sterile medicinal products and sterile active substances. However, it should be clarified that not all aspects of validation are applicable at each phase of development. For the guidance in this document related to validation, sites that manufacture Investigational Medicinal Products should apply Quality Risk Management principles to clearly define validation expectations for each phase of clinical development.</p> <p>Proposed change: Add paragraph to clarify intent. "...This Annex provides general guidance that should be used for all sterile medicinal products and sterile active substances, via adaption, using the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and pyrogen contamination associated with microbes is prevented in the final product. Where this Annex is applicable to Investigational Medicinal Products, it is recognized that not all aspects of validation may be applicable at each phase of development. For the guidance in this document related to validation, sites that manufacture Investigational Medicinal Products should apply Quality Risk Management principles to clearly define validation expectations for each phase of clinical development..."</p>
14-15	<p>Comment: The phrase "<i>associated with microbes</i>" is redundant and may reduce efforts on reduction of non-microbiological contamination.</p> <p>Proposed change: Modify language to clarify intent. "Annex provides general guidance that should be used for all sterile medicinal products and sterile active substances, via adaption, using the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and pyrogen contamination associated with microbes is prevented in the final product."</p>
17 – 22	<p>Comment: It is stated in the Scope that the requirements 'principles and guidance ... products that are not intended to be sterile (such as...)' ; we acknowledge the inclusion of this statement; however, it may not always be possible to apply such requirements to 'non-sterile products'. It is suggested to remove any 'non-sterile' products from the 'scope' of this guidance. This may lead to unnecessary confusion when the document is only aimed at 'sterile' products. Nonetheless, once adopted by PIC/s it may trigger translation to other languages and hence may lead to additional confusion and lead to increased requirement for non-sterile products.</p> <p>Proposed change: Clarify intent by replacing line with: "However While it is not a requirement, some of the principles and guidance, such as contamination control strategy, room qualification, classification, monitoring and gowning, may be used to support the manufacture of other products that are not intended to be sterile (such as certain liquids, creams, ointments and low bioburden biological intermediates) but where the control of microbial, particulate and pyrogen contamination, to reduce it as far as possible, is considered important."</p>
36	<p>Comments: Section (b) of Principles sets a requirement for personnel "attitude". It is not possible, nor necessary, to confirm or ensure proper attitudes. Behaviors would be a better word, because behaviors can be observed, while attitudes cannot.</p> <p>Proposed change: Personnel must have appropriate skills, training and attitudes behaviors with a specific focus on the principles involved in the protection of sterile product during the manufacturing, packaging and distribution processes.</p>
46-48	<p>Comment: This statement in the Principles section appears to prohibit risk assessments that are perceived as justifying a lessening of standards. This may undermine the value of risk assessments, if certain outcomes are pre-judged. The phrase: "the intent of this Annex" is vague.</p> <p>Proposed change: Modify language to clarify intent. "Risk assessments should be used to justify alternative approaches to those specified in this Annex only if provided that these alternative approaches ensure the same or greater level of contamination control of the ones described in meet or surpass the intent of this Annex."</p>
72 – 75	<p>Comment: Within the principle section, the list related work environment should also focus on organisational processes such as material- and workflows, which can be a source of contamination, if not properly designed</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	Proposed change: Add language to clarify intent. “Work environment including process and material flows” as addition to item (a) or as a separate item on list.
181 2104	<p>Comment: Section 4.2 sets a recommendation for the maximum number of operators in critical areas. However, the glossary defines Critical Area as an area designed to maintain sterility of sterile materials, sterilized product, containers, closures, and equipment that may be exposed in critical areas such as the Grade A area or a closed system. This may be interpreted as defining personnel in Grade A operations only. We suggest expanding the definition to include operators in grade B as well.</p> <p>Proposed change: Clarify intent of statement. “4.2 ... The maximum number of operators in critical grade A/B areas should be determined based on QRM principles, documented in the contamination control strategy, and validated during activities such as initial qualification and aseptic process simulations, so as not to compromise sterility assurance...”</p>
200	<p>Comment: Section 4.4 requirement for personnel to participate in a successful aseptic process simulation as a prerequisite for unsupervised entry to the Grade A/B is unnecessary and in conflict with PDA published positions, in PDA Technical Report 22 (2011) and Aseptic Processing Points to Consider Part 1 (2015). Each person entering the aseptic processing area has the potential to introduce microbiological contamination; however, the risk to product may vary with the specific job function. Personnel within an aseptic processing area present the greatest potential of microbial contamination and as such require extensive training, monitoring and on-going training to reduce the likelihood of viable particulate shedding/contamination. The critical aspects of qualification involve the ability of personnel to understand and perform their job functions, and should assure that aseptic processing area personnel have the proper training and knowledge for their respective functions. Testing through Aseptic Process Simulation is not sensitive enough to fully qualify personnel to work in the Grade A/B area. Participation in media fills does not provide additional assurance of adherence to proper clean room behavior. And mere adherence to this requirement may result in clean room personnel allowed to work in the Grade A/B area without proper knowledge and demonstration of clean room behavior. Instead we recommend an emphasis on training and monitoring, as noted in the aforementioned Technical Report and Points to Consider. In addition, as currently written, the requirement would be burdensome and limiting for certain ATMP (Advanced Therapy Medicinal Product) aseptic processes.</p> <p>Proposed change: “4.4 Only trained, qualified personnel who have passed the gowning assessment and have demonstrated their proficiency in aseptic technique by either successfully performing a qualification test entailing manual media manipulation not associated with a full aseptic process simulation (APS), or have participated in a successful aseptic process simulation test, in both cases simulating or performing their normal duties, should be authorized to enter any grade A/B area, in which aseptic operations will be conducted, or are being conducted, whilst unsupervised.”</p>
236	<p>Comment: section 4.9 states an exclusion of “mobile phones”. This may dissuade the use of new “mobile phone-like” communication technologies that would increase process control in clean room operations. Mobile devices that can be sealed from the environment or disinfected would not necessarily pose a risk to the aseptic process or product quality.</p> <p>Proposed change: Allow for technology advantages, by removing reference to mobile phone: “4.9 Wristwatches, make-up and jewelry and other personal items such as mobile phones that may pose a risk to the integrity of the clean room should not be allowed in clean areas.”</p>
330-332	<p>Comment: This paragraph in Section 5.3 implies that a Grade A (unidirectional) airflow is required within an isolator. Considering that all air within an isolator is entirely HEPA filtered and isolated from potential contamination, turbulent airflow within a closed isolator may be acceptable if supported by operational qualification demonstrating the maintenance of acceptable particulate levels.</p> <p>Proposed change: Add clarification after line 332: “Unidirectional flow within an isolator may not be required, provided that ISO 5 air borne particulate and grade A viable levels are attained.”</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
321-323	<p>Comment: Section 5.3 states prescriptive guidance for air speed as well as an expectation for justification of sampling distance. Air velocity guidance may or may not be appropriate for unidirectional flow in all cases and at all points within the Grade A zone. ISO 14644-3 clearly indicates that the test for unidirectional air flow and referencing 0.4 – 0.6 m/s should be taken within 150-300 mm of the filter face. While using the ISO guidance for qualification or re-qualification may be suitable, implication that the guidance velocity values have any validity elsewhere in the Grade A zone is not accurate. The prescription of a standard velocity is not necessary, and should depend on line and process configuration. The requirement for individual determination of standard measuring distance is not necessary, if a standard distance is already available.</p> <p>Proposed change: Remove recommended velocity, but add guidance recommendation for measurement distance. “Unidirectional air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value), the point at which the air speed measurement is taken should be clearly justified in the protocol. During initial qualification and requalification air speeds may be measured either close to the terminal air filter face or at the working height, Airflow systems that are designed to be unidirectional should provide a homogeneous air velocity as measured within 150 – 300mm of the filter face that is adequate to prevent the ingress of particulate from the less-clean surrounding environment into the working area.</p>
334-338	<p>Comment: Section 5.3 appears to restrict the interface of Grade A areas to anything but Grade B. The use of mouse holes in a properly designed operation does not add process risk and should be allowed to transfer filled and closed products from a Grade B background to lower graded environments such as Grade D zone.</p> <p>Proposed change: Modify language to clarify intent. “Grade B: For aseptic preparation and filling, this is the background environment for the Grade A zone. In general, only Grade C cleanrooms should interface with the Grade B aseptic processing area. Lower grades can be considered where isolator technology is used (refer to clause 5.19-5.20), or when mouse holes are used to transfer filled, closed products to a lower grade, and this is confirmed through air flow visualization studies and monitored the differential pressure.”</p>
351	<p>Comment: Section 5.6 requires that clean room materials must be fiber free. It would be nearly impossible to eliminate and demonstrate the elimination of all fibers from all breathable materials.</p> <p>Proposed change: Modify language to clarify intent. “5.6 Materials liable to generate fibres should not be permitted in clean areas used in clean rooms should be selected to minimize generation of fibers.”</p>
369-371	<p>Comment: We agree with the criticality for the cascade concept stated in 5.9 (a) for incoming personnel airlocks. However, there would be no risk for the higher graded environment by the bridging of zones, if there are dedicated outbound de-gowning rooms which are physically segregated from inbound gowning rooms, operate with a pressure differential, and air flow extracts generated particles.</p> <p>Proposed change: Allow for limited cascade jump of more than one grade. “a) Personnel airlocks. A cascade concept should be followed for personnel (e.g. from grade D to grade C to grade B). A cascade jump of more than one grade in a single airlock can be accepted in the event of outbound personnel traffic only, provided that the higher zone is adequately protected through differential pressure with the de-gowning room and by having adequate air patterns in this room. In general hand washing facilities should be provided only in the first stage of the changing rooms.”</p>
390	<p>Comment: The use of CNC classification as mentioned in section 5.12 (b) (iii) is not aligned with industry definitions (e.g. ISPE). Because of differing definitions and limited benefit of such a classification in modern clean room operations, we recommend removing the CNC classification designation from the document and the Glossary.</p> <p>Proposed change: Removal of CNC classification. “iii. The movement of material from clean not classified (CNC) to grade C should be based on QRM principles, with cleaning and disinfection commensurate with the risk.</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
416	<p>Comment: Section 5.12 requires the visualization of unidirectional airflow in grade A/B areas. Unidirectional airflow in grade B areas should not be a requirement.</p> <p>Proposed change: Modify language to clarify intent. “512 Air flow patterns should be visualised in grade A grade A/B areas to evaluate if airflow is unidirectional and that air from the Grade B does not intrude into Grade A.</p>
428	<p>Comment: Section 5.14 appears to require observation access to all clean room areas. If so, then design and retrofit of facilities to facilitate full visibility in less critical (i.e., Grades C and D) would be overly complicated and of questionable value.</p> <p>Proposed change: Clarify by limiting observation recommendation to grade A/B area. “5.14 Consideration should be given to designing facilities that permit observation of the Grade A/B area activities from outside the clean areas, e.g. through the provision of windows or remote camera access with a complete view of the area and processes to allow observation and supervision without entry.”</p>
450	<p>Comment: Section 5.17 appears to imply that turbulent airflow may be justified <i>only</i> in a closed isolator. However, turbulent air flow may be justifiable in certain areas within other barrier and isolator system applications such as near large pieces of equipment, stopper bowls, or mouse holes. The implication that this would not be permissible, even with proper justification, may dissuade the use of this type of barrier technology.</p> <p>Proposed change: Remove specific reference to clarify intent. Section 5.17 “...Under certain circumstances turbulent airflow may be justified in a closed isolator when proven to have no negative impact on the product...”</p>
460	<p>Comment: section 5.19 sets a requirement for grade D background environment for Isolators. Grade D background for a closed laboratory isolator may not be necessary.</p> <p>Proposed change: Clarify by limiting recommendation to production systems. “5.19 For open positive pressure production isolators or closed isolators with decontamination by a sporicidal agent, the surrounding area should correspond to a minimum of grade D.”</p>
472-478	<p>Comment: Section 5.21 requires implementation of mechanical and physical methods of glove testing “following any intervention that may affect the integrity”. This practice might adversely affect the aseptic conditions within the isolator and therefor put the sterility of a product on risk.</p> <p>Proposed change: Remove perceived requirement for mechanical/physical testing after interventions and replace with precautionary statement and inspection. “5.21 ... Glove systems, as well as other parts of an isolator, are constructed of various materials that can be prone to puncture. Integrity testing of the barrier systems and leak testing of the isolator and the glove system should be performed using visual, and mechanical or physical methods. They should be performed at defined periods, at a minimum of the beginning and end of each batch. Interventions that pose a risk to the integrity of the gloves or isolator should be avoided where possible. Where they cannot be avoided, the integrity of gloves and isolator should at least be visually inspected after such interventions.”</p>
505	<p>Comment: In the last column of Table 1 Maximum permitted airborne particle concentration during classification there is a title error. The order of the column title is wrong regarding the ISO classification “in operation/at rest”.</p> <p>Proposed change: Correct error - ISO classification “in operation/at rest” “at rest/in operation”</p>
558	<p>Comment: Section 5.29 requires periodic requalification of grade A clean room areas every six months. ISO 14644-1 and 2 recommend classification based on a risk assessment, typically at one year. Revision should be consistent with ISO 14644 recommendations.</p> <p>Proposed change: Modify language to be consistent with ISO 14644. “5.29 Clean rooms should be requalified periodically and after changes to equipment, facility or processes based on the principles of QRM, typically at not longer than one year intervals. For grade A and B zones, the maximum time interval for requalification is 6 months. For grades C and D, the maximum time interval for requalification is 12 months.</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
569-578	<p>Comment: Section 5.31 through its inclusion of “<i>More than one type of disinfecting agent should be employed</i>” appears to recommend or require the rotation of disinfectants with different antimicrobial agents. PDA position as stated in technical reports and the aseptic processing points to consider, as well as scientific literature (e.g. Akers and Agalloco PDA J Pharm Sci and Tech 2001, PDA TR-70, USP <1072>) suggests that micro-organisms would not adapt to disinfectants (in contrast to antibiotic-resistance). PDA report No. 70 infers that the pharmaceutical industry is moving away from rotation of disinfecting agents since it leads to higher residue levels, without material benefit. Cited literature: PDA TR-70 Fundamentals of cleaning and disinfection programs for aseptic manufacturing facilities. 2015, Akers, J. Agalloco, Environmental Monitoring: Myths and Misapplications PDA J Pharm Sci and Tech 2001, 55 176-184, USP 40 NF 35, chapter <1072> Disinfectants and antiseptics, PDA Points to Consider for Aseptic Processing Part 2 (2016)</p> <p>Proposed change: Removal of recommendation for multiple disinfecting agents. “...They should be cleaned and disinfected thoroughly in accordance with a written programme (for disinfection to be effective, cleaning to remove surface contamination must be performed first) More than one type of disinfecting agent should be employed, and should include the periodic use of a sporicidal agent.”</p>
580	<p>5.32 Disinfectants and detergents should be monitored for microbial contamination.</p> <p>Comments: Section 5.32 appears to require testing of all disinfecting solutions for sterility. Sterility testing for purchased, terminally sterilized disinfectants (e.g. gamma-irradiated) from qualified suppliers provides no value for quality.</p> <p>Proposed Change: Clarify recommendation only for disinfectants prepared in house. “Disinfectants and detergents, not terminally sterilized with a validated cycle, should be monitored for microbial contamination ...”</p>
619/ 2108	<p>Comment: Section 6.6 states a requirement that all critical surfaces that come into direct contact with sterile materials should be sterile. The Glossary defines Critical Surfaces as surfaces that may come into contact with or directly affect a sterilized product or its containers or closures. The Glossary further states that critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing. Based on this definition, a turntable, a star-wheel, conveyor belt must be sterile, because it contacts the exterior of sterile component, sterilized glass vials. But, these surfaces are only in contact with the outside of the glass vials, which are not product contact surfaces, and pose no risk to product sterility. Sterilization of these surfaces would be unnecessarily burdensome and potentially damaging to such systems.</p> <p>Proposed change: Clarify the intent of the recommendation by changing the definition in the Glossary: Critical surfaces: Surfaces that may come into contact with or directly affect a sterilized product. or its containers or closures.</p>
619	<p>Comment: Stopper bowls/tracks have been cited as in-direct contact surfaces in the literature (see PDA TR 22 and Aseptic Processing survey). However, the surfaces do come in contact with the portion of the stopper that contacts product, albeit to a much lesser degree and risk than container interior or fill systems. Questions and concerns have been noted by regulators regarding the ability of VHP to sterilize all interior surfaces of Isolators. However, the VHP cycle is sufficient to sterilize the low (if any) bioburden surfaces of well-designed stainless steel stopper bowls and tracks. Our proposal is to allow for sterilization or decontamination of the stopper bowls and tracks, after sterilization and installation as a risk based decision, given precautions are taken.</p> <p>6.6 All critical surfaces that come into direct contact with sterile materials should be sterile. For large equipment e.g., stopper bowls and tracks in isolators where it is not possible to pre-sterilize and install the items adequately without introducing additional contamination risk, a risk assessment should be used, including an evaluation of the effectiveness of VHP (or other treatment in-place) capability to remove all microorganisms that may be present: Precautions should be taken to ensure the effectiveness of the in place sterilization method, including:</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	<ul style="list-style-type: none"> a) Removal of any substances or residues that could reduce effectiveness of the sterilization process (e.g. oily substances) b) Pre-treatment of materials to reduce bioburden steps (e.g. offline sterilization or decontamination) c) Limited exposure of items to sources of contamination d) Monitoring and sampling of sterilized or decontaminated items at the end of the fill/ production run
672 - 676	<p>Comment: Section 7.8 notes that Water for Injections (WFI) should be produced from purified water, the WFI should be constantly circulated at 70°C, and where methods other than distillation are used, specific subsequent purification methods employed. In order to provide the flexibility of risk based options for WFI processing, these requirements and recommendations should not be exclusively expressed.</p> <p>Regarding the exclusive use of purified water: As per current EP, “Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water”. Other major Pharmacopoeias (USP, JP, FB) also consider Drinking Water quality acceptable as starting feed water to generate WFI. Common industry practice in both in the EU and the USA have many application of distillation processes by vapor compression fed by softened water and a similar number of applications using multi-effect distillation where feed water is deionized but not of Purified Water quality in terms of chemical and microbiological limits.</p> <p>Regarding the need for hot recirculation: Hot (>70°C) recirculation of WFI is not required to maintain WFI quality attributes. Recirculation at lower temperatures with periodic sanitization has been proven to be effective and validated in many instances.</p> <p>Regarding the consideration of subsequent purification methods: The April 2017 revision of EP WFI Monograph (0169) allows the use of alternatives to distillation technology to produce WFI but does not restrict these to the recommendations in the monograph. EMA has published on August 1, 2017 EMA/INS/GMP/443117/2017 “Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies final.” This document provides guidance for the application of the alternatives to distillation technology to generate WFI. Where WFI is produced by methods other than distillation alternative methods and control strategies must provide equivalent performance.</p> <p>Proposed change: Allow for more flexibility in WFI methods, where WFI quality is maintained. “7.8 Water for injections (WFI) should be produced from purified water, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C in accordance with current EP Monograph (0169) requirements. WFI should be stored and distributed in a manner that inhibits microbial growth. Recirculating systems below 70°C should be sanitized periodically based upon monitoring and risk assessment and in a manner that does not compromise WFI quality. Where the WFI is produced by methods other than distillation further techniques post Reverse osmosis (RO) membrane should be considered such as nanofiltration, and ultra-filtration alternative methods and control strategies must provide equivalent performance (ref. EMA/INS/GMP/443117/2017)</p>
688-689	<p>Comment: Section 7.12 states that hydrophobic bacteria retentive vent filters on WFI storage tanks should be sterilized, and the integrity of the filter tested before and after use. WFI storage tanks are not always equipped with microbial retentive vent filters. Hot WFI is essentially self-sanitizing and some users have successfully validated systems without vent filters. Where vent filters are employed, sterility and/or microbial retention is not a requirement because WFI in Bulk stored in the Storage tank is not required to be sterile. Such filters may be employed for bioburden control, in which case they should be sanitized, usually by steam, but not validated to be sterile. Integrity testing should be an option based on risk assessment.</p> <p>Proposed change: Modify statement to encourage risk based approach. “7,12 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters the filters should be sterilized sanitized periodically, and the integrity of the filter tested before and after use, as appropriate based upon a risk assessment.”</p>
715-717	<p>Comment: Section 7.17 recommends or requires the use of “purified water with low endotoxin” as feed to a pure steam generator. Feed water to Pure Steam generator does not require purified water to meet pure steam quality specifications. There may be no endotoxin limit (as there is no endotoxin limit for Purified Water) for a properly designed generator that has entrainment separation capability to prevent the carryover of endotoxin in the distillate.</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	<p>Proposed change: Replace current recommendation to align with clean steam generator design criteria. “7.17 Purified water, with a low level of endotoxin, should be used as the minimum quality feed water for the pure steam generator. Feed water to a pure steam (clean steam) generator should comply with drinking water standards as a minimum. Feed water should be treated and pure steam generators designed and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels. For steam generators supplying steam to moist heat sterilizers, porous hard-goods loads steam condensate must meet the compendial requirements for WFI.”</p>
751-752	<p>Comment: Section 7.24 mandates periodic cleaning and disinfection of vacuum and cooling systems. These steps should be determined on a risk basis. A risk assessment should be used to define if the periodic cleaning is needed and at which frequency, depending on the design and use of the system. For example, a closed cooling system installed outside of the clean area may not need to be periodically cleaned and/or disinfected.</p> <p>Proposed change: Modify statement to allow for a risk based approach. “7.24 There should be a risk assessment should determine if periodic cleaning/disinfection of vacuum and cooling systems is required and at which frequency.”</p>
769-773	<p>Comment: Section 8.3 mentions wide necked containers and slower speeds as higher risk operations requiring grade A environment filling. A variety of different factors contribute to the risk of product contamination during the filling operation, these are not necessarily due to slow filling speeds or the size of container openings, which may actually be more stable on the filling line. The language should reflect this and that other risks require the stated controlled environmental and filling conditions.</p> <p>Proposed change: Modify language to allow for risk based decision making. “8.3 Where the product is at an unusual risk of contamination from the environment because, for example, the 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, then the product it should be filled in a grade A zone with at least a grade C background.”</p>
815-816	<p>Comment: Table 4 is purposed to describe examples of operations and the environmental grades in which they should be performed. The requirement for steam in place as inserted under A, Aseptic Connections, seems out of place. The verbiage should be adjustment to ensure clarity.</p> <p>Proposed change: Remove wording to clarify intent. “Aseptic connections (should be sterilized by steam in place whenever feasible).”</p>
849	<p>Comment: Section 8.15 states that <i>the final sterile filtration should be carried out as close as possible to the filling point...</i> This statement requires clarification. In the case of some single use systems, the filter may not be positioned very close to the filling system. Misinterpretation of this requirement may dissuade the use of such systems or promote designs that add intervention risk.</p> <p>Proposed change: Modify language to clarify intent. Section 8.15. The final sterile filtration should be carried out as close as possible to the filling point and downstream of aseptic connections wherever possible.</p>
852 – 856	<p>Comment: Each aspect of the aseptic manufacturing process should be limited to a defined and validated duration with appropriate consideration of activities, for example cleaning and drying are often carried out as a single operation. Therefore, it should be sufficient to define meaningful hold times/maximum durations which are risk based without calling out a maximum hold time for each discrete phase.</p> <p>Proposed change: Modify language to clarify intent. “8.16 The duration for each aspect of the aseptic manufacturing process should be limited to a defined and validated maximum, including and should consider the following: Time between equipment, component and container cleaning, drying and sterilization...</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
877-881	<p>Comment: Section 8.17 recommends the use of laminar flow carts. Laminarity according to the glossary refers to an airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight-line vector. This does not occur in carts supplied with HEPA filtered air and would be difficult to show if it did. Instead, the air flow is unidirectional, meaning air cascading in one direction, but not necessarily in a laminar fashion. A requirement for unidirectional air flow will be easier to achieve, demonstrate, and more valuable for aseptic process control. Therefore, the term LAF (laminar air flow) cart should be appropriately replaced.</p> <p>Proposed change: Replace verbiage to clarify intent. “8.17 Partially stoppered vials or prefilled syringes should be maintained under grade A conditions (e.g. use of isolator technology, grade A with B background, with physical segregation from operators) or carts supplied with Grade A LAF carts air (with suitable grade B background environment and physical segregation from operators) at all times until the stopper is fully inserted.</p>
883-890	<p>Comment: Section 8.18 prescribes 100% integrity testing of containers sealed by fusion. The incorporation of a risk based approach, based on sound scientific principles is a welcome addition to the Annex. The focus should not be on end-point testing, but should embrace QRM principles with due consideration of the sealing process design, validation, and process controls.</p> <p>Proposed change: Modify language to encourage risk based decision making. “8.18 Containers should be closed by appropriately validated methods. 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. Samples of other containers and should be checked for integrity utilising validated methods and in accordance with QRM principles.” ‡ The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A statistically valid sampling plan should be utilized. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.”</p>
898-900	<p>Comment: Section 8.21 requires that equipment used to crimp vials be physically separated with air extraction. Equipment used to crimp vials do not necessarily generate particles; use of modern technologies will likely not result in the generation of large quantities of particles. The sentence should be revised to reflect this applying QRM principles together with particle data. Furthermore, the requirement for ‘adequate air extraction’ is not well defined and should be clarified (e.g. venting, vacuuming); the fundamental principle of product protection which this statement seeks to achieve is very well covered in section 8.22, justifying the removal of ‘adequate air extraction’.</p> <p>Proposed change (if any): Modify language to allow for risk based decision making. “8.21 As some equipment used to crimp vial caps can generate large quantities of non-viable total particulates a QRM approach should be taken to avoid contamination of the environment and product which may include the location of equipment at a physically separate station. the equipment should be located at a physically separate equipped with adequate air extraction”</p>
915-917	<p>Comment: Section 8.24 appears to state a requirement that is in contradiction to section 8.23 in which stoppers by process design and proven by ingress studies are integral.</p> <p>Proposed change: Modify language to clarify intent. “8.24 Where human intervention is required at the capping station, appropriate technology measures should be used to prevent stopper displacement that could lead to direct contact with the vials and to minimize microbial contamination, and which maintain the controlled capping environment.”</p>
919-920	<p>Comment: Section 8.25 infers that the use of barrier technologies minimizes human interventions. The application of RABS and isolators do not necessarily minimize human interventions, however they do minimize the risk of contamination related to those interventions</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	Proposed change: modify language to clarify intent. “8.25 RABS and isolators Barrier technologies may be beneficial in minimizing the risk of contamination from interventions. assuring the required conditions and minimising direct human interventions into the capping operation”
955-960	<p>Comment: Section 8.30 may be interpreted as requiring the use of post aseptic lethal treatments to achieve adequate assurance of sterility. As these treatments are not routine in the industry, this may lead to misinterpretation of intent. Based on the documented, successful, safe application of aseptic processing for many years, there is a lack of scientific and risk-based evidence to support the need for application of terminal sterilization or other lethal treatment processes in well designed, properly controlled and operated aseptic processes. Aseptic manufacture in these cases can provide products of suitable quality and there should be no expectation that products produced through aseptic manufacture would need the addition of some moderated ‘terminal sterilisation’ or other lethal treatment conditions. However, where there is interest in reducing the ongoing testing requirements (i.e., bioburden testing, environmental monitoring or media fills), post-aseptic processing lethal treatment options up to and including traditional terminal sterilization using moist heat or an alternate technology should be considered.</p> <p>Proposed change: Modify language to clarify intent. “8.30 Where possible, finished product should be terminally sterilized using a validated and controlled sterilization process as this provides a greater assurance of sterility than a validated and controlled sterilizing filtration process and/or aseptic processing. Where it is not possible for a product to undergo a sterilisation, consideration should be given to using terminal bioburden reduction steps, such as heat treatments (pasteurization), combined with aseptic processing to give improved sterility assurance.</p>
1008	<p>Comment: Section 8.39 requires that the carrier of product be labelled with material name. Batch number provides adequate labelling for product control and segregation eliminating the need for material name.</p> <p>Proposed change: Modify language to clarify intent. “8.39 ... Each basket, tray or other carrier of products, items of equipment or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape, or irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process...”</p>
1017-1026	<p>Comment: Section 8.41 should be modified to note that the post-sterilization assurance of sterility of an item packaged before sterilization is reliant not only upon the subsequent environment of storage but also the package design controls and sterilization process. The sterilization of items “in house” should have no different level of control or assurance of sterility.</p> <p>Proposed change. Modify language to clarify intent. “8.41 Where possible, materials, equipment and components should be contained within a sealed packaging and sterilized by validated methods appropriate to the specific material. Suitable protection after sterilization should be provided to prevent recontamination based upon QRM principles which include consideration of packaging integrity, multiple layers of packaging, handling and storage environment. The integrity of the sterile protective barrier should be qualified for a pre-established maximum hold time within the specified storage environment. If items sterilized “in house” are not used immediately after sterilization, these should be stored, using appropriately sealed packaging, in at least a grade B environment, a maximum hold period should also be established. Components Items to be used in a Grade A environment that have been packaged with multiple sterile packaging layers need not be stored in grade B (where justified) if the integrity and configuration (e.g. multiple sterile coverings that can be removed at each transfer from lower to higher grade) of the sterile pack allows the items to be readily disinfected during transfer into the grade A zone. Where protection is achieved by containment in sealed packaging this process should be undertaken prior to sterilisation.”</p>
1019	<p>Comment: The term “in-house:” is used in Section 8.41 to refer to items that are sterilized “in-house” but the use of this term and its associated requirements are clearly meant to be applicable to items that are both sterilized and then utilized for in the same facility/location for aseptic processing. These stated requirements do not apply for items sterilized “in-house” that are sold commercially. The section should clarify that “in-house” refers to items that are both sterilized and utilized in the same facility/location for aseptic processing.</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	Proposed change: Add language to clarify intent. "8.41 ... For items that are both sterilized and used for aseptic processing "in house" , if these are not used immediately after sterilization, these should be stored using appropriately sealed packaging, in at least a grade B environment for a maximum established hold time.
1042	<p>Comment: Should note that the requirements presented in Section 8.44 apply only to items that are both sterilized and used in-house for aseptic processing as these stated requirements are not applicable to items sterilized "in house" and sold commercially.</p> <p>Proposed change: Modify language to clarify intent. "8.44 Where For materials, equipment, components and ancillary items that are sterilized and used "in house" for aseptic processing, these should be sealed in packaging or containers, the integrity of the sterile protective barrier should be qualified for the maximum hold time, and the process should include inspection of each sterile item prior to its use to ensure that the sterile protective measures have remained integral.</p>
1060-1063	<p>Comment: Section 8.47 contains statements that as written apply only to porous hard goods and should be broadened to accurately cover liquid loads which use superheated water.</p> <p>Proposed Change: Modify language to clarify intent. "8.47 Moist heat sterilization utilizes clean steam or superheated water, typically at lower temperatures and for shorter duration than dry heat processes in order to sterilize a product or article. Porous hard goods Moist heat sterilization is primarily affected by latent heat of condensation through direct contact with the item and thus and the quality of steam is therefore important to provide consistent and predictable efficacy results. For aqueous liquid-filled containers, energy from moist heat is transferred through conduction and/or convection to the contents of the container without direct contact with moist heat."</p>
1089-1091	<p>Comment: Section 8.52 describes equilibration time which is not applicable to liquid loads and therefore only applies to porous hard good loads. This is not a consideration for liquid loads due to the lag in heat penetration temperature when compared to chamber temperature.</p> <p>Proposed change (if any): Modify language to clarify intent. "8.52 For porous hard goods loads, 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."</p>
1100-1102	<p>Comment: Section 8.54 may be interpreted as prohibiting moisture on any sterilized item. The presence of moisture on liquid loads products after sterilization is very common and is not a risk to sterility.-The moisture requirements in this statement are exclusively applicable to porous hard goods items.</p> <p>Proposed change (if any): Modify language to clarify intent. "8.54 ... Each item sterilized should be inspected for damage, seal and packaging material integrity. Each porous hard goods item sterilized should also be inspected and for moisture on removal from the autoclave."</p>
1114-1119	<p>Comment: Section 8.57 suggests that F₀ should be used for routine monitoring for liquid load cycles; this is only applicable when load probes are used in place of monitoring exposure time and temperature.</p> <p>Proposed change: Modify language to clarify intent. "8.57 Validation should include a consideration of equilibration time, exposure time, correlation of pressure and temperature and maximum temperature range during exposure for porous cycles and temperature, time and F₀ for fluid cycles. These critical parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of sterilization validation and, with the exception of F₀, routine cycle acceptance criteria. Where load probes are used F₀ should be part of routine cycle acceptance criteria. Revalidation should be performed annually."</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
1133-1134	<p>Comment: Section 8.60 may be interpreted as prohibiting moisture on any sterilized item. The presence of moisture on liquid loads products after sterilization is very common and is not a risk to sterility.-The moisture requirements in this statement are exclusively applicable to porous hard goods items.</p> <p>Proposed change: Modify language to clarify intent. “8.60 ... All porous hard goods load items should be dry upon removal from the sterilizer. Porous hard goods load dryness should be confirmed as a part of sterilization process acceptance.”</p>
1162-1165	<p>Comment: The terms “higher” and “lower” Grade area as presented in Section 8.65 may be confusing.</p> <p>Proposed change: Modify language to clarify intent. “8.65 ... Tunnels should be configured to ensure that airflow patterns protect the integrity and performance of the sterilizing zone, by maintaining a stable pressure differential and airflow pattern through the tunnel from the cleaner higher grade area to the less clean lower grade area.”</p>
1240-1242	<p>Comment: section 8.76 Critical process variables for validation and routine monitoring differ between conventional EO processes and process which have been approved for parametric release.</p> <p>Proposed Change: Modify language to clarify intent. “8.76 Critical process variables that should be considered as part of sterilization process validation and routine monitoring include, but are not limited to: EO gas concentration via pressure and weight displaced, relative humidity via pressure, temperature chamber pressure EO gas pressure and exposure time. The following are incremental requirements for parametric release: direct monitoring of EO gas concentration and relative humidity concentration.”</p>
1251-1261	<p>Comment: Section 8.78 may be interpreted as requiring redundant sterile filtration. The use of redundant or two-sterilizing grade filters in series, is not necessarily required and may introduce further risk through unnecessary interventions. Consequently, a company’s decision to include redundant filtration should be based on a risk-based decision. Rather than using the term ‘advisable’ which is arguably subjective and could lead to further divergences due to misinterpretation, it is proposed to clearly articulate the consideration of a second/redundant filtration in line with QRM principles.</p> <p>Proposed change: Modify language to allow for risk based decision making. “8.78 If a liquid product cannot be terminally sterilised by a microbiological process, it should be sterilised by filtration through a sterile, sterilizing grade filter (with nominal pore size of 0.22u (or less) or with at least equivalent micro-organism retaining properties), and subsequently aseptically filled into a previously sterilised container, the selection of the filter used should ensure that it is compatible with the product – see 8.119. Suitable bioburden reduction and/or sterilizing grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the primary sterilizing grade filter. Due to the potential additional risks of a sterilizing filtration process as compared to other sterilization processes, a second filtration through a sterile, sterilising grade filter (positioned as per clause 8.15), immediately prior to filling, is advisable may be considered as part of an overall contamination control strategy in line with the principles of Quality Risk Management.”</p>
1298	<p>Comment: Section 8.82 requires that the challenge organism for bacterial retention testing of filters be justified. The standard test typically used should be mentioned to avoid potential confusion and unnecessary justification efforts.</p> <p>Proposed change: Modify language to clarify intent. “8.82 ... The challenge organism used in the bacterial retention test should be justified is typically Brevundimonas diminuta (ASTM F838-15). Native and additional bioburden challenge tests should be justified.”</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
1301-1329	<p>Comment: Please review in combination with our Section 8.84 comment. The following addition could be included as part of 8.83 or 8.84. In either case, a holistic, end-to-end strategy for the control, qualification, sterilization and routine use of sterilizing filters, filter assembly's preparation, and their sterilization based upon risk would provide a significant integrated assurance of sterility. Therefore, additional language to section 8.83 is proposed.</p> <p>Proposed Change: Modify language to clarify intent. "8.83 The filter and filter assembly preparation, sterilization, and use should be qualified to ensure that the filter and assembly maintain integrity during the product sterilization process. This should include a well-documented risk based assessment of and corresponding control strategy implementation to address potential filter and assembly defects and filtration failures caused by manufacture, handling, storage, sterilization, and use of the filter and assembly prior to and during product filtration. Control strategies should include efforts to prevent such defects and failures, as well as test the filter and assembly at appropriate phases of the process, including testing prior to the filter sterilization, after use, and where the risk assessment indicates the need, after the filter sterilization. "</p>
1331-1340	<p>Comment: Section 8.84 requires an integrity test of the sterilized filter assembly prior to use, commonly referred to as the pre-use, post-sterilization integrity test or PUPSIT, in order to mitigate risk of filter failure posed by damage to the filter and assembly through sterilization and use. We feel that the use of PUPSIT methods pose their own risk to the integrity of the aseptic line and process. We feel that the risk associated with integral filter and assembly failure during use can be adequately controlled. Further, we feel that there are other means to prevent and mitigate such failure. Therefore, we offer the following proposal to satisfy concerns over filter and assembly failure, as well as concerns over the introduction of additional PUPSIT related risk.</p> <p>Proposed change: Replace current language with the following language to allow for risk based approach.</p> <p>8.84 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. It is recognised that for small batch sizes, this may not be possible; in these cases an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved. There should be written integrity test methods, including acceptance criteria, and failure investigation procedures and justified conditions under which the filter integrity test can be repeated. Results of the integrity tests (including failed and repeated tests) should be included in the batch record.</p> <p>"8.84 The filter and filter assembly preparation, sterilization, and use for sterilization of the product should be qualified to ensure that the filter and assembly maintain their integrity throughout the entire process. This should include a well-documented risk based assessment of and corresponding control strategy implementation to address potential filter and assembly defects and filtration failures caused by manufacture, handling, storage, sterilization, and use of the filter and assembly prior to and during product filtration. Control strategies should include efforts to prevent such defects and failures, as well as test the filter and assembly at appropriate phases of the process, including testing prior to the filter sterilization, immediately after use, and where the risk assessment indicates the need, after the filter sterilization.</p> <p>8.85 Filter and assembly integrity methods and systems should be designed, installed and operated to be effective for their purpose and where appropriate, fit for use in an aseptic process and controlled environment. There should be written integrity test methods, including acceptance criteria, failure investigation procedures and justified conditions under which the filter integrity test can be repeated. Results of the integrity tests (including failed and repeated tests) should be included in the batch record."</p> <p>Note: We do not intend to modify the current version of section 8.85. Therefore, if accepted, the subsequent section numbers should change accordingly.</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
1319	<p>Comment: Section 8.83 lists “flow rate” as a filtration parameter that should be considered in validation and routine processing. During bacterial challenge validation of a filter, flow rate <u>or</u> pressure can be kept constant as both parameters may not be validated simultaneously (see PDA, Technical Report 26, Section 6.2). It therefore should be assessed whether flow rate <u>or</u> pressure should be validated and controlled in routine use. This is also in alignment with USP 1229.4 “Filtration conditions” and EP chapter 5.1.1 “Membrane Filtration, Routine control”. Therefore, as both parameters correlate to each other “pressure <u>or</u> flow rate” should be included for routine and validation.</p> <p>Proposed change: Modify language to clarify intent. “8.83, c) iv. Flow rate or pressure”</p>
1349-1352	<p>Comment: Section 8.87 requires integrity testing of all filters in the “filter train”. It would be difficult if not impossible to perform post sterilization, pre- use filter integrity testing (AKA PUPSIT) on multiple filters in the train without design changes and manipulations that would likely add risk to the process.</p> <p>Proposed change. Modify language to clarify intent and reduce risk. “8.87 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. Pre-use testing of the sterilized filter assemblies may not be required, due to the complexities of the testing procedure.”</p>
1354-1358	<p>Comment: The instruction regarding bioburden sampling requires clarification to ensure consistency with existing guidance.</p> <p>Proposed Change: Modify language to clarify intent. “8.88 Where a redundant sterilizing filter is used, the additional filter does not require post integrity testing unless the primary sterilizing filter fails, in which case the redundant filter must then satisfactorily pass post-use integrity testing. For routine commercial manufacturing, bioburden testing should be performed on the bulk solution, immediately before its sterile filtration. If a presterilising, redundant filter is additionally installed, then sampling for bioburden testing may be performed prior to the prefiltration, provided that no holding time is scheduled for the solution between the two filtration steps. Bioburden samples should be taken prior to the first filter and the sterilizing filter, systems for taking samples should be designed so as not to introduce contamination.”</p>
1360-1362	<p>Comment: Section 8.89 does not take into account campaigns as often used in API manufacturing. Also, the actual duration of the filtration should be always validated to ensure the effectiveness of the filtration process.</p> <p>Proposed change: Modify language to clarify intent. “8.89 Liquid sterilizing filters should be discarded after the processing of a single lot, unless validated for multiple use, including the duration of filtration. The same filter should not be used for more than one working day unless such use has been validated.”</p>
1418-1421	<p>Comment: Section 8.97 may be interpreted as requiring environmental monitoring in critical areas of rotary BFS machines. The rotary machine does not have a grade A area, because the parison is closed and the air of the container/parison is blown with sterilised air by sterile filtration. Clarification is needed to avoid confusion over whether the intent is to have companies attempt to monitor in a closed parison system, which would be impossible or, where attempted, risky and disruptive.</p> <p>Recommended change: Modify language to clarify intent. “Section 8.97: For Rotary-type equipment the background environment should comply with the viable and non-viable limits “at rest”. It is not normally possible to perform environmental monitoring within the parison during operation or at rest. Monitoring of the background environment should be performed in accordance with risk management principles.</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
1427-1429	<p>Comment: Section 8.96 states that for Shuttle-type equipment, the environment should comply with the viable and non-viable limits at rest and the viable limit only when in operation. The shuttle zone should meet grade A viable limits. Yet Section 8.99 may be interpreted as contradicting that recommendation, by requiring grade A for the area between parison cutting and mould sealing, critical zone. PDA Points to Consider for Aseptic Processing Part 2 (2016) recommends grade A for the BFS critical zone, but defines that critical fill zone as the area where the sterile product is filled into the container. The open parison transport environment should be controlled and monitored to protect the interior and exterior of the container from contamination during transport. Consideration of clean air flow should be designed to minimize the risk of ingress of contamination, without creating excessive turbulence or unintentional cooling of the exposed parison which may interfere with the protection of the open, formed containers within the moulds provided by the rising heat from the cut parison and could result in container formation and seal difficulties.</p> <p>Proposed change: Modify language to clarify intent. “8.99 In addition, for Shuttle-type designs, the critical fill zone, area between parison cutting and mould sealing should be covered by a flow of HEPA filtered or sterile air of appropriate quality to provide grade A at the critical zone.”</p>
1460-1461	<p>Comment: Section 106 requires sterilization of the lyophilizer before each load. Under certain circumstances, which may include but are not limited to the use of automated lyophilizer loading/unloading technologies, RABS for lyophilizer loading/unloading, a successful history of aseptic process simulations and sterility assurance, the sterilization frequency of lyophilizers may exceed after each load. In addition, excessive sterilization cycles may cause quicker aging and damaging of the lyophilizer. A frequency of sterilization based upon QRM principles is therefore suggested as implied in ISO standard 13408 – 3, Aseptic processing of health care products (Part 3:Lyophilization).</p> <p>Proposed change: Modify language to allow for risk based approach. “8.106 The lyophilizer should be sterilized according to a predetermined frequency defined based on a risk assessment which takes into consideration technology and controls related to loading and unloading, to prevent contamination between cycles before each load. The lyophilizer should be protected from contamination after sterilization.”</p>
1488-1490	<p>Comment: The intent of Section 8.111 is not clear. We recommend a modification of language to clarify that utensils used during the manual loading and unloading of lyophilizers routinely come in to proximity or are touched by operators and should be sterilized.</p> <p>Proposed change: Modify language to clarify intent. “8.111 ... e) Utensils used during transfer to, for the manual loading and unloading of, the lyophilizer (such as trays, bags, placing devices, tweezers, etc.) should be subjected to a validated sterilization process”</p>
1532	<p>Comment: Section 8.118 states that single use systems involve a specific risk as a result of an <i>increase in number and complexity of manual operations and connections made</i>. This is not necessarily the case. There may be less or as many connections, but these connections may be intrinsic (sterile aseptic) connectors, which are likely to be less risky than non-intrinsic connections</p> <p>Proposed change: Remove language to correct statement. “Section 8.118, e) Increase in number and complexity of manual operations and connections made.”</p>
1614	<p>Comment: The statement made in section 9.17 would be better placed in Section 9.5, because it is a general comment for all environmental monitoring, not just in the total particulate (non-viable section)</p> <p>Proposed change: Clarify intent by moving the sentence in line 1678-1680 and enter combine it with Section 9.5.</p> <p>“9.17 The monitoring of grade C and D areas in operation should be performed in accordance with the principles of QRM to provide sufficient data to allow effective trend analysis. The requirements and alert/action limits will depend on the nature of the operations carried out.”</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	<p>“9.5 Routine monitoring for clean rooms, clean air devices and personnel should be performed “in operation” throughout all critical stages, including equipment set up. The locations, frequency, volume and duration of monitoring should be determined based on the risk assessment and the results obtained during the qualification. The monitoring of the areas in the ‘in operation’ state should be performed in accordance with the principle of QRM to provide sufficient data to allow effective trend analysis.</p>
1629-1631	<p>Comment: Section 9.9 mentions grade B, C, and D, but not grade A. Alert levels <i>for total particles</i> should also be set in grade A.</p> <p>Proposed change: Add language to clarify intent. “9.9 The alert levels for grade B, C and D should be set based on the area performance, with the aim to have levels lower than those specified as action levels, to minimise risks associated and identify potential changes that may be detrimental to the process.”</p>
1637	<p>Comment: Section 9.11 suggests a requirement for surface monitoring of critical surfaces during production. The monitoring of surfaces should be at the end of the batch or campaign to avoid the risk of media residue left on critical surfaces in grade A or the performance of a potentially risky intervention during the production of a batch.</p> <p>Proposed change: Modify language to reduce risk of contamination. “9.11 Surfaces should be monitored at the end of the batch or campaign, and personnel should be monitored after critical operations. Results from monitoring should be considered when reviewing batch documentation for finished product release.”</p>
1651	<p>Comment: As per the points made in our General comments section, update title and content of Table 5, replacing the words/terms “limit” and “non-viable” with the words/terms “level” and “total particulate” respectively, and the deletion of “contamination”.</p> <p>Proposed Change: Modify wording to reflect intent. “Table 5: Recommended limits levels for airborne particle concentration for the monitoring of total particulate non-viable contamination”</p>
1651	<p>Comment: The significant figures are not consistent (5 µm vs 5.0 µm) in table 5 and Note 2. If this is not intentional, please use consistent significant figures throughout the document.</p> <p>Proposed change: Add significant figures to numeric values presented in table to clarify intent.</p>
1653 and 1659	<p>Comment: Table 5 sets limits for 5 µm particle monitoring for Grade A environments. Limits should not be applied for ≥5 µm particle monitoring for Grade A environments, due to the sampling limitations, as noted in ISO 14644-1.2:2014, which states, “<i>Sampling and statistical limitations for particles in low concentration make classification inappropriate... Sample collection limitations for both particles in low concentration and particles greater than 1 micrometer make classification of this particle size inappropriate, due to potential particles losses in the sampling system.</i>” Relying on such limits may result in decisions made based on unreliable scientific data. It would be more effective to recommend that companies focus on the overall trend of ≥5 µm particle monitoring rather than individual numbers based on the low accuracy of the measurement. It should also be noted that clean room environmental performance issues, anticipated by the ≥5 µm particle monitoring, would be well represented with ≥ 0.5 µm particle monitoring. Therefore, there is a low risk of an issue arising that would be missed due to the lack of absolute ≥5 µm particle monitoring limits.</p> <p>Proposed change (if any): Reduce over-reliance on scientifically questionable monitoring method by altering requirement for ≥5 µm particle monitoring. Eliminate the ≥5 µm particle monitoring column in Table 5 and replace with a line stating: When companies count particles ≥5 µm separately, they should focus on the overall trend rather than individual numbers. Procedures should be in place to monitor and establish actions to be taken when excursions in such trends occur.</p>
1671-1676	<p>Comment: Section 9.16 mentions “similar” system. It is not clear what is meant by “similar” system. We would recommend deletion of this sentence to avoid confusion. We further recommend, based on our General comment on the use of “limits” and “levels”, that the wording at the end of the section be modified to be more appropriate for “alert levels”</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	<p>Proposed change: Delete wording to avoid confusion. “9.16 It is recommended that a similar system be used for grade B zones although the sample frequency may be decreased. For grade B zones the design of the monitoring system should be based on risk assessment and be commensurate with the risk of the process to the product sterility assurance. The grade B zone should be monitored at such a frequency and with suitable sample sizes that the programme captures any change in levels of contamination and system deterioration. If alert limits are exceeded, alarms should be triggered. Exceedance of alert levels should be responded to as defined during the design of the environmental monitoring programme.</p>
1703-1707	<p>Comment: If modified, Table 5 recommendation makes 9.22 redundant. Therefore, if Table 5 comment is accepted, we recommend the deletion of this section.</p> <p>Proposed change (if any): If the recommendation posted for Table 5 is accepted, then Section 9.22 should be deleted. “9.22 Although monitoring of $\geq 5.0 \mu\text{m}$ 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.”</p>
1720-1722	<p>Comment: We believe that the intent of “such as” in Section 9.25 was to encourage a risk based option for the environmental monitoring. However, as written, it may be interpreted as requiring that all the listed methods are used. Some of these methods, e.g. settling plates, may not fit well with newer technology, may be of limited value, and may add unnecessary interventions. There is also a redundancy notes for glove prints, as personnel monitoring is addressed earlier in the personnel sections.</p> <p>Proposed change: Modify language to add clarity to intent and allow for risk based determination. “9.25 Where aseptic operations are performed, microbiological monitoring should be frequent using a use a selected combination of methods, but not necessarily all; such as settle plates, other passive air methods, volumetric air, glove print and surface sampling (e.g. swabs and contact plates).</p>
1728-1733	<p>Comment: Section 9.27 requires the use of full duration monitoring in grade A and B areas. Continuous monitoring of some grade B areas e.g. storage rooms might not be of value. QRM methods should be used to determine in which grade B areas continuous monitoring would be of value and should be performed.</p> <p>Proposed change: Modify language to clarify intent. “9.27 Continuous monitoring in Grade A and B areas should be undertaken for the full duration of critical processing. QRM-principles should be used to identify where continuous monitoring is necessary in Grade B ensuring that the monitoring scheme is commensurate with the risk of the process to the product sterility assurance. The monitoring should include including equipment (aseptic set up) assembly and filling operations i.e., an understanding of function and interactions of each clean area and 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.</p>
1735-1736	<p>Comment: Section 9.28 refers only to rapid microbiological monitoring systems. This should be broadened to anticipate other technology.</p> <p>Proposed change: Add wording to allow for other methods where appropriate. “9.28 Rapid/alternative microbial monitoring methods may be adopted after validation as long as they are demonstrated to be at least equivalent to the established methodology”</p>
1747	<p>Comment: As per the points made in our General comments section, update title and content of Table 6, replacing the words/terms “limit” and “non-viable” with the words/terms “level” and “total particulate” respectively, and the deletion of “contamination”.</p>

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	Proposed Change: Modify wording to reflect intent. “Table 6: Recommended microbial maximum limits levels. for microbial contamination. ”
1768-1772	<p>Comment: Section 9.33 may be interpreted as requiring speciation in all cases. It may not be possible, or practical to identify to species level in some cases. Therefore, we recommend the addition of qualifying wording: “if possible”.</p> <p>Proposed change: Clarify by adding qualifying wording. “9.33 If microorganisms are detected in a grade A or B zone, they should be identified to species level, if possible, and the impact of such microorganisms on product quality (for each batch implicated) and state of control should be evaluated. Consideration may also be given to the identification of grade C and D contaminants and the requirements should be defined in the contamination control strategy.”</p>
1791	<p>Comment: Section 9.35 (a) mentions all aseptic operations. For clarity, to the point where the container is sealed should be added.</p> <p>Proposed changes: Add wording to clarify intent. “a) Process simulation tests should assess all aseptic operations performed subsequent to the sterilisation of materials utilised in the process to the point where the container is sealed.”</p>
1796-1797	<p>Comments: Section 9.35 (c) states a requirement for performing anaerobic media fills when manufacturing is performed in a strict anaerobic environment. The term “strict anaerobic environment” is open to interpretation and if considered as a complete absence of oxygen it is impossible to practically achieve. The principle of a process simulation incorporating an anaerobic environment is to detect microorganisms which might be present during routine manufacture where genuine anaerobic conditions are experienced. Under such manufacturing conditions a diverse variety of microorganisms exhibiting varying levels of oxygen tolerance and growth requirements might contaminate the process. Although the human skin borne aerotolerant anaerobe <i>Propionibacterium acnes</i> might represent a greater risk of process contamination the level of oxygen tolerated in the process may be higher than 0.5% for strict anaerobes (Loesche, 1969) ⁽¹⁾. Therefore, the process simulation test should recognize and assess this risk, developing as far as practicably possible conditions permitting the detection of anaerobic microbial contamination. Accordingly, the wording should be changed. (1) Loesche, W.J. (1969) Oxygen sensitivity of various anaerobic bacteria. Appl. Microbiol., 18(5), 723-727.</p> <p>Proposed change: Clarify intent. “c) Where aseptic manufacturing is performed under in a strict anaerobic conditions a risk-based assessment should be used to determine the environment should be evaluated with an appropriate anaerobic media and conditions in addition to aerobic evaluation.</p>
1806	<p>Comment: Section 9.35 (f) requires full duration cycle aseptic process simulations for lyophilized processes. There is no value to mimic the full cycle duration time (can be 40-50 hrs). Instead it is important to include parts that would challenge the freeze dryer the most e.g. vacuum pulses to challenge the microbe ingress into the chamber and transport into the vials due to turbulence during the vacuum pulses. This must be assessed via a risk assessment. According to recent PDA survey (PDA’s Aseptic Processing Survey, 2017) most companies today are simulating the cycle during APS using a 2 hours dwell time with one or more vacuum pulses to challenge the microbe ingress into the chamber and transport into the vials due to turbulence during aeration during the vacuum pulses.</p> <p>Proposed change: Modify to allow for risk based approach. “f) The process simulation test for lyophilized products should include the entire aseptic processing chain, including filling, transport, loading, chamber dwell, unloading and sealing. The process simulation should duplicate mimic the lyophilization process, with the exception of freezing and sublimation, including partial vacuum and a dwell time (determined by a risk assessment of the process and the equipment) cycle duration and parameters as appropriate for the media</p>

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1813-1820	<p>Comment: Section 9.36 (a) and (b) is unclear as to frequency and number of interventions, and may lead to misinterpretation. The process simulation testing should include inherent and corrective interventions based on a risk assessment and where appropriate, proportional to how many times they occur in production.</p> <p>Proposed change (if any): Modify to clarify intent and allow for risk based approach. “9.36 The process simulation testing should take into account various aseptic manipulations and interventions known to occur during normal production as well as worst case situations include inherent and corrective interventions determined based on a risk assessment and where appropriate, proportional to how often they occur during routine production. including:</p> <p>a) Inherent interventions at the maximum accepted frequency per number of filled units. b) Corrective interventions in representative number and with the highest degree of intrusion acceptable.</p>
1834-1836	<p>Comment: Section 9.38 (b) only discusses the use of bracketing in regards to container/closure configurations. The container/closure configuration should be regarded as an example as there may be other situations as well.</p> <p>Proposed change: Modify language to include other bracketing options. “b) Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or a matrix approach can be considered for initial validation of certain configurations the same e.g. container/closure and other configuration.</p>
1845	<p>Comment: Section 9.38 (e) appears to set a requirement in the aseptic simulation study for ensuring that any contamination is detectable. This would be difficult if not impossible. Process simulations use general microbial growth medium (or surrogate) to recover and culture microorganisms present. It is widely recognized that such growth medium is limited in that it will not recover, culture and detect all microorganism or microbial contaminants present (Epstein, 2013)⁽¹⁾. The process simulations test plan should recognize this risk and develop as far as practicably possible conditions permitting the detection of microbial contamination. Accordingly, the wording should be changed.</p> <p><i>(1) Epstein, S.S., (2013) The phenomenon of microbial uncultivability. Curr. Opin. Microbiol., 16(5), 636-642.</i></p> <p>Proposed change (if any): 9.38 (e) Ensuring that as far as practically possible any contamination is detectable.</p>
1850 - 1854	<p>Comment: Section 9.38 (g) sets a requirement for full duration media fills. Full duration media fills may not be necessary and may lead to decisions based on invalid scientific information, the setting of production batch duration merely on results of APS, and a false sense of security in regards to the length and conditions of production runs. As noted in the (2016) PDA Aseptic Processing Points to Consider Part 2, Contamination of an aseptic process is primarily a function of events rather than time. Therefore, the duration of the process simulation should be sufficient to assess the performance of those activities identified in a risk assessment as having the potential to introduce contamination. The duration of the process simulation should be risk based and designed to simulate the conditions which provide the greater likelihood of uncovering process contamination (i.e., worst case conditions). Each company should determine appropriate risk based rationale and approaches applicable to their unique operations by means of documented risk assessment and process simulation design.</p> <p>Proposed change: Modify language to allow for risk and science based approach. “g) The duration of the process simulation filling run to ensure it is conducted over the maximum permitted filling time. If this is not possible, then the run should be risk based and sufficient duration to challenge the process, the operators that perform interventions, and the capability of the processing environment to provide appropriate conditions the manufacture of a sterile product.</p>
1875-1880	<p>Comment: It is not clear what is meant by recovery rate in Section 9.39. Due to large volumes used in API sterile manufacturing it may not be possible to evaluate all the simulated material used. The simulation material should be</p>

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	<p>suitable to ensure an evaluation of the process without compromising microbial recovery. Wording has been updated to reflect this.</p> <p>Proposed changes: Modify language to clarify intent. "9.39 ... In addition, all the simulated materials (surrogates of growth medium) should be subjected to microbiological evaluation. The recovery rate from simulation materials should be sufficient to satisfy the evaluation of the process being simulated and should not compromise the recovery of micro-organisms."</p>
1881	<p>Comment: Section 9.40 requires three aseptic process simulation tests to be run for each shift. Shift changes are elements of the process itself, but do not represent process changes. Therefore, as inferred in PDA TR 22, they should included in the study design, but not necessarily require addition runs.</p> <p>Proposed change: Modify language to clarify intent. "Section 9.40. Process simulation tests should be performed as initial validation, generally with three consecutive satisfactory simulations for each aseptic process and filling line covering all shifts, and after any significant modification to the HVAC system, equipment, major facility shut down, process and number of shifts, etc... "</p>
1882-1889	<p>Comment: Section 9.40 states that process simulations should be performed as <i>initial validation</i>. This may be incorrectly interpreted as meaning the APS is all that needs to be done to validate the aseptic process. It may be more accurate to say "... as part of the initial validation..."</p> <p>Proposed change: Modify language to clarify intent. "9.40 Process simulation tests should be performed as part of the initial validation, generally with three consecutive satisfactory simulation tests per shift, and after any significant modification to the HVAC system, equipment, major facility shut down, process and number of shifts, etc."</p>
1925	<p>Comment: Section 9.45 states that APS units should be incubated in clear containers. This may not always be practical and clear units may not run the same as pigmented units. It is not necessary to incubate in clear container. However, it is necessary to read or inspect them in clear container. We recommend modifying the language to note the distinction.</p> <p>Proposed changes: Modify language to clarify intent. "9.45 Filled APS units should be incubated in a clear, transparent container, where possible or be transferred to a transparent container after incubation to ensure visual detection of microbial growth."</p>
1935-1942	<p>Comment: Section 9.47 does not include a recommendation that full implementation of corrective actions should be completed before additional APS and production resumes.</p> <p>Proposed change (if any): Modify language to clarify intent. "9.47 In the case of a failed process simulation there should be a prompt review of all appropriate records relating to aseptic production since the last successful process simulation. The outcome of the review should include a risk assessment of the non-sterility for batches manufactured since the last successful process simulation, and the justification for the disposition of batches of product affected. Subsequent to a failed APS, in addition to a full investigation, and the implementation of corrective action production should resume only upon further successful APS unless adequately justified. The number of repeat successful APS prior to resuming production should also be justified.</p>
1954-1956	<p>Comment: Section 10.1 states that starting material microbiological contamination should be minimal. Clarifying the expectation would be helpful. Minimal may be open to interpretation. And starting materials (unless sterile) can contain levels of bioburden that, providing it is not objectionable by the species/type and or quantity may not adversely affect the process, intermediate or final product quality attributes. In addition, the use of the term</p>

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	<p>"starting materials" in drug product manufacturing may create confusion with its definition in biologics manufacturing. ICH Q11 defines starting materials specifically as cell banks for biologics and starting materials for APIs. We recommend replacing "starting materials" with "drug substances, excipients and raw materials".</p> <p>Proposed change: Add language to clarify expectation. "10.1 10.1 Microbiological contamination of starting materials should be minimal. Specifications of the starting material drug substances, excipients and raw materials should include requirements should include requirements for microbiological quality when the need for this has been indicated by monitoring and/or by the contamination control strategy."</p>
1966-1968	<p>Comment: Section 10.4 refers exclusively to endotoxins. However, not only bacterial endotoxin but other microbially-derived molecules are known to be and have been shown to be pyrogenic, representing patient risk. This should be recognized in the text.</p> <p>Proposed change (if any): Modify language to clarify intent. "10.4 For parametric release systems, the bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate, the level of pyrogens endotoxins should be monitored as identified in the contamination control strategy."</p>
1978-1988	<p>Comment: Change to: Section 10.7 item (c) indicates a requirement for separate sterility testing performed on individual sterilization loads of the same product batch. The assurance of sterility is dependent upon an effective control strategy for the entire sterile product manufacturing process and successful/passing results of a sterility test is neither scientifically nor statistically valid in the support of sterility for terminally sterilized products which require a Probability of a Non-Sterile Unit (PNSU) $\leq 10^{-6}$. This section 10.7 (c) defines a batch as a sterilizer load and thus requires sterilizer load-based finished product sterility test plans which unnecessarily increase the testing burden and the associated likelihood of potential false positive results while providing no practical benefit in the support of products terminally sterilized to a PNSU $\leq 10^{-6}$. When risk is taken into consideration for sample determination, then it is important to note that it is common practice to develop terminal sterilization processes with large safety margins with a qualification/requalification approach and associated critical processing parameters that are identical across all sterilizers within a given facility. Additionally, an increase in sterility test samples on this scale does little to increase the practical sensitivity of the sterility test in support of a PNSU $\leq 10^{-6}$ for terminally sterilized products.</p> <p>Proposed Change: Delete section 10.7 item (c). Each sterilized load should be considered as different batches and require a separate sterility test.</p>
1985-1986	<p>Comment: Section 10.7 (b) suggests that sterility test samples should be taken from the potentially coolest part of the load. Cycle development and qualification studies can provide significant information and data, beyond 'cold spots' which may provide insight on which product units are most scientifically valuable for sterility testing. Under certain circumstances, coolest part of the load may not be apparent or relevant. Therefore, while coolest part of the load should be a consideration, other factors may provide more valuable scientific information.</p> <p>Proposed change: Modify language to allow for flexibility in choosing most scientifically valid samples. "10.7 (b) Products which have been heat sterilized in their final containers, consideration should be given to data from cycle development, qualification studies and risk assessments to support the sampling plan. determine which samples to take, e.g. from the potentially coolest part of the load." Where process knowledge indicates that the coolest part of the load is relevant to the process performance and product quality, samples should be taken from that part of the load.</p>
2002-2005	<p>Comment: Section 10.10 may be interpreted as requiring that environmental monitoring data be regarded as batch release specifications. Environmental monitoring limits should not be regarded as specifications. Misinterpretation of this recommendation by users could result in unnecessary batch rejection. As stated in the (2015) PDA Aseptic Processing Points to Consider: <i>Microbiological and particulate environmental monitoring data generated in Grade A/B environments should be reviewed as part of the batch-release process. Microbiological and particulate</i></p>

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	<p><i>environmental monitoring data from lower-grade areas may also be considered. Environmental monitoring results that exceed an established action level in Grade A/B areas should be investigated and reviewed, and the risk to product safety should be evaluated. A microbial count excursion of an established level, even in Grade A/B zones, does not, by itself, mandate a batch rejection, provided that the investigation determines that there is no impact on product quality and safety. Excursions from action levels in lower-grade areas also require investigation, and this investigation may include impact on batch release.</i></p> <p>Proposed change: Revise language to avoid misinterpretation of intent. “10.10 Environmental monitoring data generated in grade A and B areas should be reviewed as part of product batch release. A written plan should be available that describes the actions to be taken when data from environmental monitoring are found out of established levels or out of trend. or out of specification.”</p>
2018	<p>Comment: PDA strongly supports the definition and use of the terms “Alert and Action Levels”, as noted in the Glossary. We recommend that “Alert and Action Levels” be used throughout the text and tables in the body of the document, rather than “Alert and Action Limits”.</p>
2042	<p>Comment: Glossary definition for “bacterial retention testing” notes <i>Brevundimonas diminuta</i> at a minimum concentration of 10⁷ Colony Forming Units/ml. It should be 10⁷ Colony Forming Units/ sq. cm.</p> <p>Proposed change: Correct units designation. “Bacterial retention testing – This test is performed to validate that a filter can remove bacteria from a gas or solution. The test is usually performed using a standard organism, such as <i>Brevundimonas diminuta</i> at a minimum concentration of 10⁷ Colony Forming Units/ml sq. cm.”</p>
2045	<p>Comment: The Glossary definition of “Bioburden” is the total number of microorganisms associated with a specific item prior to sterilization. There may be other sources of bioburden other than those associated with sterilized items.</p> <p>Proposed Change: Broaden the definition, as published in PDA Technical Report 69, Bioburden and Biofilm Management in Pharmaceutical (2016), to clarify intent. “Bioburden - The total number of microorganisms associated with a specific item prior to sterilization. Viable microorganisms associated with personnel, manufacturing environments (air and surfaces), equipment, product packaging, raw materials (including water), in-process materials, or finished products.”</p>
2023	<p>Comment: Notwithstanding the line 2018 comment, the definition of “Action Level” includes “when exceeded”. It would be more meaningful to change to “when reached”.</p> <p>Proposed change: “Action Level - An established microbial or airborne particle level that, when exceeded reached, should trigger appropriate investigation and corrective action based on the investigation.”</p>
2037	<p>Comment: Definition of “Asepsis” is that it is a state of control ... that <i>precludes</i> microbiological contamination of the exposed sterile product. <i>Preclude</i> is usually defined as preventing from happening or making impossible. That will be difficult to achieve and demonstrate.</p> <p>Proposed change: Modifying definition to allow for more practical control measures. “Asepsis - A state of control attained by using an aseptic work area and performing activities in a manner that precludes minimizes the potential for microbiological contamination of the exposed sterile product.”</p>
2076	<p>Comment: The use of CNC classification as mentioned is not aligned with industry definitions (e.g. ISPE). Because of differing definitions and limited benefit of such a classification in modern clean room operations, we recommend removing the CNC classification designation from the document and the Glossary.</p> <p>Proposed change: Remove Glossary entry. “Clean Non-Classified (CNC) area – An area that does not meet any of the formal pre-determined grades of cleanliness included in the Annex, i.e. grades A to D, but where a manufacturer defined level of microbial control is still required. The area should be subject to a formal cleaning/disinfection regime”</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	<p>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 within each CNC area."</p>
New line	<p>Comment: As noted in our General comments section, definitions for "Contamination" should be aligned to ICH Q7A.</p> <p>Proposal: Clarify revision intent by adding a definition to the Glossary. "Contamination - The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens), or of foreign particle matter, into or onto a raw material, intermediate, drug substance or drug product during production, sampling, packaging or repackaging, storage or transport, with the potential to directly adversely impact product quality."</p>
New line	<p>Comment: As noted in our General comments section, definitions for "Contamination" should be aligned to ICH Q10.</p> <p>Proposed change: Clarify revision intent by adding a definition to the Glossary. "Contamination Control Strategy - A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."</p>
2232	<p>Comment: SAL or sterility assurance level, in the Terminal sterilization glossary definition (and elsewhere in the revision) should be replaced with the more technically-precise and descriptive term: PNSU or probability of a non-sterile unit. While the terms SAL and PNSU are synonyms, both are characterized by a reference to a condition or level of non-sterility which is expressed as the probability of a single viable microorganism occurring on or in an item after sterilization. On that basis, PNSU is the more accurately descriptive term. Consistent with the approach that is used for Alert and Action Levels, a mathematical symbol (e.g., \leq) or descriptive phrase (less than or equal to) should be used in place of the term "better" for use with the term probability of a non-sterile unit. The exponent of 10^{-6} for PNSU should always be preceded by the symbol "\leq" or the phrase "less than or equal to". Example: PNSU $\leq 10^{-6}$.</p> <p>Proposed change: Modify definition to use PNSU terminology. "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 (PNSU) of $\leq 10^{-6}$ sterility assurance level (SAL) of 10^{-6} or better (i.e. the theoretical probability of there being less than or equal to one a single viable microorganism present on or in a sterilized unit is equal to or less than 1×10^{-6} (one in a million))."</p> <p>In addition: The PSNU definition should be added to the Glossary:</p> <p>Probability of a Non-Sterile Unit (PNSU): The number that expresses the probability of occurrence of a non-sterile unit after exposure to a sterilization process. Within the pharmaceutical industry, a design end point of less than or equal to the probability of one non-sterile unit in a million units is expected, i.e., PNSU $\leq 10^{-6}$. [Synonym: Sterility Assurance Level (SAL)].</p>