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July 13, 2020
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Reference: Annex 1 Revision: Manufacture of Sterile Medicinal Products

Dear European Commission:

PDA appreciates the opportunity to provide comments to the February 2020 revision of Annex 1 and continues to support its development. This revision is an extremely important update representing the most recent and relevant guidance for the manufacturing of sterile pharmaceuticals, being applied well beyond the EU by both the industry and Non-EU inspectorates. The inclusion in the Annex 1 Working Group (WG) of experts from the European Commission, the World Health Organisation (WHO) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a welcomed directional move towards a global harmonization of requirements.

This Annex and the guidance it presents will have a great impact on the global industry and product supply for years to come. The EMA set a key objective in its 2015 Annex 1 revision concept paper, to embrace the use of new technologies to prevent detrimental impact on product and to encourage the introduction of new technologies that are not currently covered. The recent pandemic and related drug shortages has further reinforced the importance of the developing and implementing sustainable, effective, modern manufacturing methods to produce sterile product of uncompromised quality. To meet this objective, the Annex must have the clarity and strong scientific foundation to promote innovation, encourage process improvement, and ensure beneficial change. But it must also have the clarity of intent to avoid the non-beneficial modification of manufacturing operations, the addition of unneeded complexity, and the possibility of unnecessary manufacturing/supply disruption. We believe the changes will help EMA achieve its stated objective.

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. PDA recommendations were prepared by a committee of experts in sterile pharmaceutical manufacturing, taking into consideration comments received from other subject matter experts, its international membership, and the industry at large. Many of our recommendations have been influenced and reinforced by input received during the workshops, conferences and meetings PDA held throughout the 2017-2020 Annex revision review process.

PDA has attached a table with general and specific comments, recommendations, and justification to further clarify the points made herein. The comments were peer reviewed and approved for use by the PDA Science Advisory Board and PDA Board of Directors consisting of pharmaceutical manufacturing experts. They are based on the goal of assisting in the development of a guidance document that:

- clearly communicates the expectations, minimizing misinterpretation
- is based on scientific knowledge
- encourages innovation and the use of new technologies
- provides for the use of risk assessments in evaluating the applicability of specific requirements
- promotes the prevention of failures, rather than primarily relying on testing and detection

The revision represents significant progress towards this goal. We see much improvement and acceptance of earlier comments. However, because of the complexity of the subject matter, the varying experience of companies, and the interpretation of ancillary inspectorates relying on the Annex, additional clarification is needed. In the absence of modification, there are concerns that some sections of the Annex will create confusion and uncertainty for both the industry and inspectors leading to a focus of resources away from areas where advancements have the greatest impact on both improving the manufacturing process and ensuring long term product supply.

As part of the commenting process, we identified and wish to point out some important concerns that should be further addressed, including (more details are in the comments form):

1. The use of prescriptive requirements and examples (perceived as prescriptive requirements), that may restrict or limit current and future innovative approaches.

2. Mixed messaging on the allowance of alternative approaches based on risk, by alternating a language supporting a risk based approach with very prescriptive requirements.

3. A focus on reactive process monitoring and product testing as a primary means of process control, that results in less emphasis on process design, training and failure prevention.

4. The need for recognition of the impact and feasibility of certain Annex requirements and changes to existing manufacturing processes, facility, and operations, as compared the product quality benefit of those requirements and changes.

5. The need to clarify the intent of and harmonize language in Annex sections, to prevent misunderstandings due to the wide geographical scope of this guidance document

6. The lack of clear distinction between and the perceived grouping of technologies that requires different contamination control strategies, including RABS and isolators, terminal sterilization and aseptic processing, and ATMPs and conventional therapy manufacturing.

Many of the topics presented in the Annex are complex and reflect the need for further discussion and the evaluation of scientific evidence to reach an optimal state of control. Foremost among these is the practical means to achieve contamination free conditions for larger indirect product contact surfaces in isolators, QRM approaches for sterile filtration control and PUPSIT, and best uses and limitations of Aseptic Process Simulations. We encourage a continued dialog with this body, the industry, and other health authorities to further clarify and refine these and other topics in this important Annex.

PDA continues to be committed to assisting in the development of this importance guidance. Upon completion of the revision we remain commitment to assist the EMA (PIC/S and WHO) with any educational, training, or communication efforts required to ensure the correct interpretation and implementation of the principles, recommendations, and requirements presented in the Annex. If there are any questions or any further assistance we can provide, please do not hesitate to contact me.

Kind regards,

Richard M. Johnson

Richard Johnson
President & CEO, PDA
CC: SANTE-Revision, EC, Jahanvi (Janie) Miller, PDA

SECOND TARGETED STAKEHOLDER CONSULTATION

GMP
Revision on Annex 1
Manufacture of Sterile Products

1. Introduction

The current annex 1 is being reviewed to better ensure the sterility of medicinal products placed on the market for the benefits of patients. The revision was notably necessary to facilitate implementation of the principles of relevant ICH guidelines, to extend the underlying concepts to include new areas of technology and processing not previously covered and also to clarify areas that have been highlighted as ambiguous due to the age of the document.
In order to maintain the global alignment of standards, achieving at the same time assurance for the highest quality, the Annex 1 Working Group (WG) is made of experts from the European Commission, the World Health Organisation (WHO) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).
A first draft of the revised Annex 1 was published for public consultation from 20 December 2017 to 20 March 2018.
Following the contribution of about 140 stakeholders and after processing more than 6200 comments the WG issued a revised document, version 12, in December 2019.
Due to widespread interest from industry following the first public publication of the Annex 1, it was found necessary to engage with stakeholders in a second targeted consultation on the updated draft guidance, version 12.
The second consultation aims at collecting experience from the sectors on certain changes proposed and concerns raised. The associations representing the sectors were therefore contacted and are expected to provide a contribution.

The draft guideline of version 12 provided has been formatted with prescribed line and page numbers.

To submit feedback, please provide it exclusively using this dedicated template below.

2. Scope of the consultation

This second consultation is intended to be focused and limited to paragraphs that raised concerns or were changed more significantly, as identified below.

2.1. Feedback on the concerns raised by stakeholders

	Qualification & requalification c	from § 4.25 to 4.35
	Handling of water systems	from § 6.7 to 6.15
	Integrity testing of large volume	§ 8.21
	Handling of sterilizing filter incl	§ 8.88 and 8.95 & 8.96
	Handling of lyophiliser	from § 8.110 to 8.113
	Sterility testing	§ 10.6 & 10.7

2.2. Sections and/or paragraphs which were substantively modified

	Definition and handling of barrie	from § 4.18 to 4.24
	Handling of gas filters	from § 6.18 to 6.20 and 8.89 & 8.90
	Personnel qualification & gownir	§ 7.5 & 7.6 and from 7.14 to 7.16

	Aseptic production	from § 8.11 to 8.19	
	Moist heat sterilisation	from § 8.54 to 8.65	
	Personnel monitoring	§ 9.32 & 9.33	
	Aseptic process stimulation (APS	§ 9.34 & 9.40 & 9.47	
	Quality control	§ 10.1	
2.3. Other significant comments			
	Please avoid re-submitting comments which you already submitted at the first consultation	All document	
3. Name and contact details of the reviewing organisation			
Please don't add any personal information as the comments might be published			
4. Comments			
Please write your comments using the spreadsheet below			
Line number (s)	Comments	Suggested text	Justification
2.1. Feedback on the concerns raised by stakeholders			

396-417	As currently worded, the section may be mis-interpreted as requiring all of the bulleted list be performed on re-qualification and as well initial qualification of the clean room, when the intent is for it to be initial qualification.	Cleanroom qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. As part of the qualification requirements of Annex 15, the initial qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation). i. Installed filter leakage and integrity testing. ii. Airflow measurement - Volume and velocity. iii. Air pressure difference measurement. iv. Airflow direction and visualisation. v. Microbial airborne and surface contamination. vi. Temperature measurement. vii. Relative humidity measurement. viii. Recovery testing. ix. Containment leak testing (where relevant) As per Annex 15, the inclusion of tests for requalification should be justified and the criteria for evaluation defined.	'Initial' has been added to the second sentence in the paragraph to clarify that the requirements listed are expected for the initial qualification and not necessarily for periodic requalification. It is important to reinforce that these tests provide valuable information to qualify and confirm the reliability of performance of the clean room. However, once qualified, the evaluations and analysis of on-going monitoring should provide evidence that the clean room continues to perform to specified levels. A sentence has been added to the end of the paragraph reinforcing the need to justify requalification criteria. 'Where relevant' has been added to the final bullet point in the list to clarify that containment leak testing is only needed where containment is required.
426-427	As currently written, the section may be mis-interpreted as requiring the monitoring of a larger particle size, which may not align with supplier recommendations and may not be scientifically beneficial.	For cleanroom classification, the airborne particulates equal to or greater than 0.5 and 5 µm should be measured. For Grade A zone and Grade B at rest, classification should include measurement of particles equal to or greater than 0.5 µm; however, measurement using a second, larger particle size, e.g. 1 µm in accordance with ISO 14644 may be considered. This measurement should be performed both at rest and in operation. The maximum permitted airborne particulate concentration for each grade is given in Table 1.	The reference to 1 µm has been removed, because monitoring that size particle may not be scientifically beneficial. Most particle counters are calibrated according to ISO 21501. This norm states that during the verification of the size setting, the error in the particle size can be up to +/- 10%. Further one, the counting efficiency of a particle counter with a minimum detectable size of 0.5 µm, will only be between 100 +/- 10 % for 1 µm particles. By using a second particle size of 1 µm, the obtained values will not be robust as the results will reach the capability of the particle counter itself.
446-461	As currently written, the section may be mis-interpreted as recommending the use of the APS for all in operation classification tests of the clean room, instead of offering it as an option for certain personnel related tests. The section may also be mis-interpreted as setting an arbitrary limit of 15-20 minutes for the clean room clean up period. In general, the concept presented are acceptable but need clarification.	i. The definition of "at rest" state is the condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as specified and standing by for operation, without personnel in the room. ii. The definition of "in operation" state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer's defined operating mode with the maximum number of personnel present performing or simulating routine operational work. In operation classification may be performed during simulated operations and certain aspects of the classification confirmed during aseptic process simulations (where worst case simulation is required). iii. The particulate limits given in Table 1 above for the "at rest" state should be achieved after a "clean up" period on completion of operations. The "clean up" period should be determined during the classification of the rooms, documented and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation. (guidance value of 15 to 20 minutes).	The change clarifies the option for portions of the classification studies to be performed during the aseptic process simulation. While it is an established principle of process validation, that all critical operating systems be qualified prior to the performance of the APS, it may be practical to perform certain aspects of the classification involving presence of clean room personnel during the APS. In addition, the guidance value for cleanup period has been replaced with language linking the determined value to process operation requirements. The current value of 15 to 20 minutes, while not unreasonable is arbitrary and may limit the use of technology in the future. Instead, the important requirement to incorporate whatever value is determined in clean room procedures is emphasized. Substitute the term "airflow velocity" for "air speed" throughout the document. "Speed" does not define direction while "velocity" does, and, of course, direction is critical to our purpose.

463-470	As currently written, the section may be mis-interpreted as requiring the prescribed guidance value. In addition, as currently written, the section may be misinterpreted as requiring air velocity measurement for non-Grade A zones. In addition, some of the language referring to air speed requires clarification.	The speed acceptable range for velocity of air supplied by Grade A unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Airflow speed velocity should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working height (e.g. where high risk operations and product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement. Grade A Unidirectional airflow velocity should be correlated to airflow visualization studies.	"Speed" has been replaced with "velocity" or velocity related terms, because it refers to a vector quality including both speed and direction. "Grade A" has been inserted in the section, because unidirectional flow may pertain to other than Grade A areas; therefore, it should be clear that these requirements are meant for Grade A and not necessarily for any and all unidirectional airflow system. The section stating the guidance range has been removed, because it may be considered by some to be a prescribed range and limit. Airflow velocity should be designed, measured and maintained to ensure that, where it is specified, appropriate unidirectional air movement provides protection of the product and open components at the working height. However, the most suitable velocity range is highly dependent on several factors other than airflow velocity. These include: • the individual production equipment calling for Grade A protection • the individual Unidirectional Air Flow Device, UDAF, supplying air • the geometries of the room in which the equipment and UDAF is situated Prescribing air flow velocity ranges changes focus from the importance of understanding and evaluating the effectiveness of the flow in terms of protecting the product and critical surfaces. Note that the target interval is a historic one that does not align with current ISO guidance. The proof of concept for the airflow velocity is in the air flow visualization. The correlation between velocity measurements and visualization is key when velocity is used to verify continued compliance with the visualized airflow.
471-492	As currently written, the section may be mis-interpreted as relying on the qualification to set or establish microbial contamination levels, rather than to confirm that the adequacy of the controls in place to maintain acceptable environmental conditions.	Environmental monitoring during clean room qualification should demonstrate that the maximum level of microorganisms is not exceeded. The microbial concentration of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment, including the results of the classification, air visualization studies and knowledge of the process and operations to be performed in the area. The maximum limits for microbial contamination levels during qualification for each grade are given in Table 2. Qualification should include both at rest and in operation states. Table 2: Limits for microbial contamination during qualification (a) Settle plates should be exposed for the duration of operations and changed as required after 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used. (b) It should be noted that for Grade A, the expected result should be no growth. Note 1: All of the types of methods indicated for a specific Grade in the table should be used for qualifying the area of that specific Grade. If one of the methods is not used, or alternative methods are used, the approach taken should be appropriately justified. Note 2: Limits are applied using cfu throughout the document. If different or new technologies are used that present results in a manner different from cfu, the manufacturer should scientifically justify the limits applied and where possible correlate them to cfu. Note 3: For qualification of personnel gowning, the limits given for contact plates and glove prints in Table 7 should apply. Note 43: Sampling methods should not pose a risk of contamination to the manufacturing operations.	The first sentence has been replaced to clarify and avoid misinterpretation of the intent of the section. The qualification should confirm the control of microbiological activity in the clean room, not determine or establish those levels. "Of the types" has been added to Note 1 to reinforce that it is the type of monitoring that is important, rather than the specific test. This is needed to allow for the use of alternative methods that may be more effective or more appropriate for a given manufacturing technology today or in the future. Note 3 has been removed, because it pertains to personnel qualification and monitoring, and section 4.33 addresses clean room qualification.

494-513	As currently written, the requirement for requalification intervals for Grade C and D areas is more stringent than ISO 14644 requirements.	The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requirement for requalification of cleanroom areas is as follows: Table 3: Minimum test requirements for the requalification of cleanrooms <image001.jpg> * performed according to a risk assessment documented as part of the CCS. However, required for filling zones (e.g. when filling terminally sterilized products) and background to Grade A RABS. For Grade A & backgournd B areas, the maximum time interval for requalification is 6 months. For other Grade B areas, the maximum time interval for requalification is determined in the range from 6 to 12 months in the CCS. For Grade C & D areas, the maximum time interval for requalification is 12 months. For Grade C & D areas, the frequency of the integrity test can be reduced based on good historical performance. Results of routine Environmental Monitoring can be integrated in the requalification data. Appropriate testing requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out-of-compliance equipment or facility condition or after changes to equipment, facility or processes. The significance of a change should be determined through the change management process. Examples of changes to be considered include but are not limited to the following: i. Change in the operational use of the cleanroom, or of the operational setting parameters of the HVAC system. ii. Interruption of air movement which affects the operation of the installation. iii. Special maintenance which affects the operation of the installation (e.g. change of final filters).	The interval for Garde C and D area requalification should be based on risk-based assessment rather than fixed intervals. Where regular microbial monitoring of clean rooms is based upon QRM principles and the monitoring sites are equivalent to those that are employed in initial qualification the addition of microbial monitoring during area re-certification is unnecessary. ISO-14644-2 recommends annual re-classification of clean rooms and allows for a reduction in frequency based upon continued satisfactory performance.
633-638	As currently written, the section states a requirement for prevention of biofilm, which may not be feasible using current technology.	Water produced should comply with the current monograph of the relevant Pharmacopeia. Water treatment plant and distribution systems should be designed, constructed and maintained to minimize the risk of particulates, microbial contamination/proliferation and pyrogens (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs), and prevent minimize the risk of formation of biofilms to ensure a reliable source of water of an appropriate quality. Where filters are included in the system, special attention should be given to the monitoring and maintenance of these filters. Water produced should comply with the current monograph of the relevant Pharmacopeia.	The last sentence has been moved to the front of the paragraph to emphasize that the primary objective of section 6.7 is to present some of the criteria for producing water meeting Pharmacopeia quality standards. Therefore, it is important to emphasize that objective by opening the section with that statement. All that follows helps guide the reader on the means to meet that objective. The word "prevent" has been replaced with the word "minimize", because it may not be possible and may be misleading for companies to think these steps will prevent biofilm formation. However, it is important that they take actions to minimize the potential formation and then diligently review and monitor the effectiveness of those actions.

646-651	As written the use of examples are often misinterpreted as prescriptive and exclusive requirements, which may limit the use of alternate, innovative, or improved approaches, available and forthcoming.	Water for injections (WFI) should be produced from water meeting specifications, in compliance with the current monograph of the relevant Pharmacopeia, that have been defined during the qualification process, stored and distributed in a manner which minimizes the risk of microbial growth (for example by constant circulation at a temperature above 70°C). Where the WFI is produced by methods other than distillation, further techniques such as nanofiltration and ultra-filtration as well as electrodeionization (EDI) should be considered and validated in conjunction with reverse osmosis (RO) membranes.	Pharmacopoeias do define the specs for feeding water (USP -Drinkable Water, EP -Drinking 0r Purified Water, China- Purified Water) for WFI plants. Also, the design of the water system must take into account the quality of the feed water and the required characteristics after the treatment (WFI). The proposed change removes the two sets of examples. It is important to note the use of nanofiltration and EDI may be detrimental and produce additional challenges.
653-655	As currently written, the section sets a requirement for sterilization of vent filters that may not be feasible or necessary.	Where If WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should be sterilized sanitized and the integrity of the filter tested before installation and after removal following use.	'Sterilized' has been replaced with 'sanitized', because air vent filters should be hydrophobic but need not be microbially retentive nor do they need to be sterile. WFI is by definition non-sterile and common storage conditions effectively eliminate microbial growth. Where QRM dictates the use of a microbially retentive filter, it should be integrity tested periodically to ensure its functionality. The use of vent filters to limit ingress of contaminants should be subject to the principles of QRM. Filter effectiveness by means of integrity testing, where applicable, should be performed. Test results should be interpreted, and appropriate actions taken based upon the risk to water quality and to the ultimate quality of the product.
657-661	To minimize the risk of biofilm formation, sanitization of water-treatment and storage/distribution systems should be carried out according to a predetermined schedule or when microbial counts exceed action limits. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure and water should be tested and released for use according to written procedures after disinfection/regeneration.	To minimize the risk of biofilm formation, sterilization sanitization or disinfection or regeneration of water systems should be carried out according to a predetermined schedule and when microbial counts exceed action limits. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure and water should be tested after disinfection/regeneration. The results should be approved before the water system is returned to use.	Sanitization is used in place of disinfection/regeneration because it is BROAD term which allows for the establishment of microbial limits based on QRM principles. Regeneration and sanitization of water pre-treatment steps (filtration, carbon treatment) would not usually comply, not should they be expected to, with the commonly accepted definition of disinfection (e.g., a specified multi-log reduction). The suggested wording also distinguishes water treatment from storage/distribution. It allows for the common practice of continuous rather than periodic sanitization of storage/distribution, such as by hot circulation. Approval of the water after chemical sanitization of treatment steps and prior to use may be according to a written procedure that is based on a validated process.

663-673	Currently as written this section may potentially be too prescriptive and may hinder periodic sampling of all points which could be more effective than sampling of one point.	Regular ongoing chemical and microbial monitoring of water systems should be performed. Alert levels should be based on the qualification or a review of ongoing monitoring data that will identify an adverse trend in system performance. Sampling programs should reflect the requirements of the CCS and may include: i. All points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis. ii. Potential worst case sampling locations. iii. A sample from at least one varied point of use the point at the end of the distribution loop each day that the water is used.	The inclusion of the word "may" allows for latitude in determining the optimal sampling plan depending on process design and operation. The change to subsection (iii) allows for varied daily sampling. The reason that end of loop is removed is that by definition the loop is a continuous process flow circuit, where if designed and operated consistently, any one point of use should have no higher risk than another. The primary purpose of daily sampling is then to uncover an unforeseen or new variable in the system. Therefore, periodic sampling of all points would be more effective than sampling of one point.
1016-1024	As currently written this section may be misinterpreted as needing 100% integrity testing of the inner bad over sealed permanently sterilized products; which is not feasible.	Containers should be closed by appropriately validated methods. i. Containers closed by fusion, e.g. Blow-fill-seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing, or where 100% integrity testing is shown to be not feasible, should be taken and checked for integrity using validated methods. ii. Samples of containers closed by other methods, should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically valid sampling plan should be utilized. The sample size should be based on information such as supplier approval, packaging component specifications and process knowledge. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.	It is not currently feasible to perform 100% integrity testing on all of stated the product configurations. For example, many flexible containers (i.e., LVP/SVP bags) are placed in overpouches prior to terminal moist heat sterilization to ensure that liquid product formulation attributes are stable over the shelf life of the product. With the currently available 100% integrity testing technologies, the application of 100% integrity testing represents a destructive test as the overpouch would be required to be removed from units after sterilization for testing. Although an additional overpouch could be reapplied after testing, this represents an unnecessary and excessive burden. Additionally, moisture present on product (from rinses after filling or from moist heat sterilization) can often interfere with test results of the currently available integrity test methods (e.g., vacuum decay, mass transfer, etc.). Due to these examples and the lack of compatibility of current integrity test methodologies, the pharmaceutical industry is not currently prepared to adopt 100% integrity testing for all of the stated container configurations. Preliminary results from the Kilmer Conference PAT and Current Moist Heat Practice to Demonstrate Sterility Assurance Survey (full results to be published at a later date) provide further confirmation of a lack of ability and readiness of the pharmaceutical industry to adopt the 100% integrity testing requirement. For flexible containers, only 1 Respondent (8.3%) currently employed 100% integrity testing while 7 Respondents (58.3%) indicated that it would take 2 or more years to implement this requirement.

1486-1512	While the section is much improved from previous versions, there remain points requiring further clarification. These include, the need to emphasize the QRM objective of the section, the removal of examples which may be mis-interpreted as exclusively prescribed requirements, the evaluation of risk to aseptic processing if posed by PUPSIT, and some technical modifications	Within the risk-based design of the sterile filtration process, The the integrity of the sterilized filter assembly should be verified assured. This may be done by integrity testing before use, to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. Integrity test limits should correlate to the microbial retention capability of the filter established by the filter supplier during qualification. Test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that pre-use post sterilization integrity testing (PUPSIT) may not always be possible advisable after sterilization due to process constraints design (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of non-sterility. Points to consider in such a risk assessment of the sterile filtration process should include but are not be limited to: i. In depth knowledge and control of the sterilization process to ensure that the potential for damage to the filter is minimized. ii. In depth knowledge and control of the supply chain to include: • Contract sterilization facilities. • Defined transport mechanisms. • Packaging of the sterilized filter, to prevent damage to the filter during transportation and storage. iii. In depth process knowledge such as: The specific product type, including particulate burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test. • Pre-filtration and processing steps, prior to the sterilizing filter, which would remove particulate burden and clarify the product prior to the sterile filtration. • Risk to the aseptic process	Sterilizing grade filtration is a critical process which requires a comprehensive, end-to-end risk-based design. Emphasis should be put on prevention of failures throughout all the filter lifecycle. It is acknowledged that integrity testing of the filter assembly is an important step to confirm effectiveness of the filtration process. It is generally recognized that post-use filter integrity testing is sufficient to detect filter failure and ensure patient safety unless there is a possibility that a filter passing the post-use test could have allowed bacterial penetration during filtration. This possibility is the phenomenon referred to as filter "flaw masking", hypothesized to occur when, for example, a filter is damaged during sterilization such that it allows bacterial penetration, but that the damage becomes plugged during the filtration process to such an extent that it allows the filter to exhibit a passing post-use integrity test result. For this masking phenomenon to occur, two conditions must exist: first, there must be a flaw in the filter that is large enough to allow bacterial penetration during use, yet small enough to be plugged during the filtration process. Second, the product being filtered must be capable of blocking that flaw to the extent that it will pass a post-use integrity test. Studies have been performed and data collected by PDA and the Biophorum consortium to identify when such masking circumstances may occur, and as such when performing a Pre-Use, post sterilization integrity testing is advisable. These studies show that the occurrence of potential masking conditions would be extremely rare, predictable and controllable. [ref. PDA/Biophorum draft masking study and BCT papers]. Integrity test immediately after filter sterilization can help identify filter issues before use, however such test per se add complexity to the process and can elevate the risk of product contamination due to the additional manipulations downstream of the sterilizing filter. PDA and Biophorum conducted a series of industry surveys and prepared a comprehensive PUPSIT Best Practice Points to Consider report that presents levels of complexity that can pose a risk to the aseptic process. In addition, PDA and Biophorum assessed risks posed by filter manufacturing and usage that indicate adequate levels of control. [ref. PDA/Biophorum draft Capstone article, FTA's and Best Practice PTC]. A comprehensive control strategy should consider all the above and identify the most suitable approach for each product and manufacturing process, and the preventive measures and controls to be in place from the filter manufacturing, to its sterilization and use, up to the post-use testing, to ensure product sterility. In addition, the integrity test limits are established by the filter manufacturer during their qualification activities and not during the process validation at the end-user site. The amended sentence creates clarity to that point.
1537-1538	As currently written, the section may be misinterpreted as requiring filters be discarded after each lot during a multiple lot campaign.	Liquid sterilizing filters should be discarded after the processing of a single lot unless validated for campaign manufacture and the same filter should not be used for more than one working day unless such use has been validated.	Provision for multiple lot campaigns has been added to the section, because there are specific filtration processes, which utilize the filter for more than one batch, for a campaign. That campaign use has to be process validated, meaning proof has to be given that the filter will function as specified over the entire campaign.

1654-1658-	As currently written, the section could be mis-interpreted as requiring the APS to include the time between the start and end of multiple sterilization processes and holding times. Or the downtime between sterilization cycles when the lyophilizer is not used and not supposed to remain sterile.	The sterilization of lyophilizers and associated equipment, (e.g. trays, vial support rings) should be validated and the holding times between sterilization cycles and the start of loading should be included in the appropriately challenged during aseptic process simulations. The lyophilizer should be sterilized regularly, based on system design. Re-sterilization should be performed following maintenance or cleaning. Sterilized lyophilizers and associated equipment should be protected from contamination after sterilization.	The conditions and time between the end of a given lyophilizer sterilization and the start of the loading of that lyophilizer is the critical aspect of the process that should be addressed in the section. Clarification of what is the intended holding time referenced in the section and included in the aseptic process simulation is important.
2290-2308	As currently written, the section may be misinterpreted as requiring additional sterility testing after any intervention. In addition, as currently written, the section implies that it is feasible and scientifically beneficial to test samples from "worst case" locations throughout a terminally sterilized product load.	The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example: i. For products which have been filled aseptically, samples should include containers filled at the beginning, middle and end of the batch and after an activity or event assessed to pose a risk to the sterility of the product, where the testing of product immediately after the activity and event would provide valuable information for determining its impact on product sterility. any significant intervention (e.g. interventions where the integrity of a barrier is breached (open door)) or an operator intervention into critical zones. ii. Where worst-case locations have been identified in the sterilizer or load Ffor products which have been heat sterilized in their final containers, samples taken should be representative of these locations. worst-case locations where (e.g. for sterilizers with defined the potentially coolest or slowest to heat part of each load). iii. For products that are lyophilized, samples taken from different lyophilization loads. Note: Where the manufacturing process results in sub-batches that represent an increased or variable risk to product sterility, (e.g. for terminally sterilized products) then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests.	Explanation for proposed change to section 10.6 (ii): Although some sterilizers contain identified and even designed (e.g., prevacuum sterilizer drain) slower to heat locations or coldspots, not all sterilizers contain consistent worst-case locations due to sterilizer and process design. Examples of sterilizers that may not contain consistent worst-case heat-up locations include some waterspray and water immersion sterilizers which feature active water circulation to ensure a uniform distribution of the heating medium across the sterilizer and product. Explanation for proposed changed to section 10.6 Note: The statistical and detection sensitivity limitations of the finished product sterility test are well-known, and it is universally accepted that this test is incapable of providing support for a 10-6 Sterility Assurance Level for terminally sterilized products. Section 10.5 appropriately emphasizes the achievement of critical parameters as the primary means for demonstration of product sterility. In the development of any sampling plan, the principles of QRM must be employed to ensure proper product representation to support the effective disposition for any product attribute including sterility. In situations where multiple sterilizers (properly maintained, operated, calibrated and qualified) are utilized with an identical recipe of sterilizer parameters to sterilize product from a single batch, the level of risk mitigation provided by performing a sterility test on each sterilizer load for a batch provides an insignificant incremental level of assurance of sterility when compared to a sterility test involving at least a single product unit from each sterilizer load from the batch. An increase in the number of samples associated with a requirement for a full sterility test for sublots of a batch represents an unnecessary proliferation of a scientifically flawed practice without providing an associated patient benefit commensurate with this increased burden of testing. The requirement for sterility test after "any significant intervention" is replaced in subsection (i) with risk assessment language encouraging the understanding of the intent and benefit of the test. The proposed change clarifies the use of sterility test after interventions, with proper assessment and CCS understanding, while avoiding the following unintended consequences of the current language. Without the proposed change, some companies and others would have trouble defining a "significant intervention", opting instead for pulling sterility samples after interventions that pose little risk and with little benefit. Because the removal of intervention samples involves an activity in or near the critical zone, this activity itself poses a risk to the sterility of product. (2) Without the proposed change, some companies and others will rely on the sterility test as the indicator of the appropriateness of the intervention and its effect on subsequent filled product. It is important for companies to understand that the sterility test is a statistically limited analysis designed to certify the batch, it is not designed to be a means to evaluate the appropriateness or performance of process activities or interventions. Confidence in the appropriateness of interventions, activities, and control measures should be obtained through process design, performance and monitoring, rather than testing of product. (3) Without the proposed change, some companies will re-define, or re-categorize activities in the critical zones as something other than interventions, in order to avoid performing additional sterility tests, therefore not performing other controls and assessments needed for such interventions
2.2. Sections and/or paragraphs which were substantively modified			

322-325	Section 4.18, as currently written, may be interpreted as presenting RABS and isolators as equal technologies. In addition, section 4.18, as currently written, may be interpreted as limiting the technology available for transfer of materials to rapid transfer and transfer isolators. The mention of only two systems, may dissuade companies from exploring and using innovative solutions.	Isolator or RABS, which are two distinct technologies, and the associated processes, should be designed to provide protection of the Grade A environment from contamination. The entry of materials during processing (and after decontamination) should be minimized and preferably supported by systems that prevent contamination.	The first change reinforces that it is important for the reader to recognize that while RABS and isolators are both barrier systems used to separate personnel from the aseptic process, they are two very distinct technologies and the controls required for both are different. The second change allows for the use of support systems and procedures beyond those specifically mentioned, thus allowing for innovative approaches that are or may be available.
332-340	Section 4.20, as currently written, sets a requirement for unidirectional airflow in open isolators, where it may not be necessary or in some cases not feasible to have traditional unidirectional airflow due to the confined space and configuration.	In operation, The the critical zone of the a RABS or open isolator used for aseptic processes should meet Grade A requirements where with unidirectional airflow. The critical zone of an isolator in operation should meet Grade A requirements, and where the process design and controls require, have unidirectional airflow. In isolator systems where airflow may not be unidirectional, it should provide Grade A conditions and be demonstrated to provide adequate protection for exposed products during processing. The design of the RABS and open isolators should ensure a positive airflow from the critical zones to the supporting background environment; (unless containment is required in which case localized air extraction is required to prevent contamination transfer to the surrounding room). Negative pressure isolators should only be used when containment of the product is considered essential and risk control measures are applied to ensure the critical zone is not compromised.	"In operation" has been added to the first sentence to clarify that RABS critical zones should meet Grade A and be unidirectional air during operation. The reference to open isolators has been removed from the first sentence and the second sentence modified to include both open and closed isolators, and requiring unidirectional airflow where needed, because most open isolators are essentially closed, with openings only for the removal of sealed product. In these systems, it is not necessary or in some cases not feasible to have traditional unidirectional airflow due to the confined space and configuration. Filtered air, with proper flow and pressure, that is not unidirectional can still provide required level of cleanliness and Grade A conditions in well designed and decontaminated isolators. The strict requirement for unidirectional airflow in all isolators will be difficult to achieve and demonstrate; and may have the unintended consequence of dissuading the development and use of innovative isolator designs that use smaller critical spaces. Smaller critical spaces are important, because they are less complex and limit exposure of product to environment. The proposed change removes the limitation of unidirectional airflow for isolators, thus allowing for use of innovative isolator technology and designs.
342-345	The section, as currently written, uses language that is not consistent with terms used in section 4.22. The section also seems to indicate that open door interventions may be performed on or in isolators.	For RABS used for aseptic processing, the background environment should meet at least correspond to a minimum Grade B and airflow studies (e.g. airflow studies) should be performed to demonstrate the absence of air ingress during interventions, such as door openings for RABS and open isolators. The background environment for open isolators should meet correspond to Grade C or D, based on a risk assessment.	The proposed change replaces "meet" with "corresponds to" – in order to be consistent with the wording used in section 4.22 and eliminates the potential misunderstanding of open-door interventions.

347-351	As currently written, the section may be mis-interpreted as pertaining only to closed isolators.	The background environment of a closed isolator should correspond to a minimum of Grade D. The disinfection/decontamination programme should be included as a key consideration when performing the risk assessment for the CCS of an open and closed isolators. Where additional process risks are identified, a higher grade of background should be considered. The decision as to the supporting background environment should be documented in the CCS	The change clarifies the intent of the section by adding closed and open isolators.
353-363	The PDA expert committee found this section difficult to understand and open to interpretation. This is an important section containing valuable guidance and clarification would be beneficial. There is also a concern that the section as written may be misinterpreted as requiring the use of mechanical methods to test the integrity of fixed RABS gloves after interventions.	The materials used for glove systems in isolators and RABS should have mechanical and chemical resistance adequate for their purpose. The materials used for glove systems (for both RABS and isolators), as well as other parts of an isolator, should be demonstrated to have good mechanical and chemical resistance. The frequency of glove replacement should be based upon risk of failure, defect rate, and criticality of usage as defined within the CCS. The isolator exterior barrier should be tested to confirm absence of air leakage and the integrity of fixed gloves used in isolators and RABS should be confirmed by tests or other methods demonstrated to be suitable for the task and criticality of the glove design and usage. Integrity testing of the barrier systems, and leak testing of the glove system and the isolator should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined periods based on an assessment of process and product risk. The integrity of fixed gloves should be tested at a minimum upon installation, at the beginning and end of each batch or manufacturing campaign, and after an activity assessed to pose a risk to the integrity of the fixed glove. Where RABS are located in Grade B area with environmental controls in place and the presence of test instrumentation may add risk during manufacturing, visual examination may be used to test the integrity of the fixed gloves between batches. The testingshould be performed at defined periods, at a minimum at the beginning and end of each batch, and should include a visual inspection following any intervention that may affect the integrity of the system. For single unit batch sizes, integrity may be verified based on other criteria, such as the beginning and end of each manufacturing session. RABS gloves used in Grade A zone should be sterilized before installation and sterilized (or effectively decontaminated by a validated method which achieves the same objective) prior to each manufacturing campaign. The frequency of glove replacement should be defined within the CCS.	The changes have been made to reinforce the use of risk-based approaches. Because of the RABS design and placement in the clean room, use of instruments and equipment need to perform mechanical integrity testing of gloves may compromise the aseptic processing environment and sterility of product. The proposed change presents the section in a more understandable flow and clarifies the requirement for inspection of gloves after some interventions or during a campaign. There is also a concern that integrity testing of isolator gloves during a batch or campaign would inflate and may over-pressurize gloves which may pose a risk to the integrity of the fixed glove. It is also noted that for both RABS and isolators it may not be possible to do a physical integrity test during the batch or campaign without a risk to product sterility.

710-716	As currently written, the section sets a requirement for placement of gas filters at point of use, which may not always be feasible or advisable. In addition, the section requires microbiological monitoring of the gas, which may not be necessary for properly designed and integrity tested systems.	Gases used in aseptic processes should be filtered through a sterilizing filter (with a nominal pore size of a maximum of 0.22 µm) at point of use located so as to minimize the number of aseptic connections required between the sterilizing filter and the point of use. Where the filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results included as part of the batch certification process. Any transfer pipework or tubing that is located after the final sterilizing filter should be sterilized. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.	'At point of use' has been replaced with risk-based language to allow for more effective process design and align with product filter location related language appearing elsewhere in the Annex. The requirement for monitoring has been removed, because sterilizing filters that have been validated for gas service and are integrity tested to ensure effectiveness, should obviate the need to monitor the gas for microbial contamination.
758-765	Section 7.5 represents an improvement over previous language. It contains important guidance and points for industry. However, during the PDA expert committee review, it became apparent that there remained significant points where clarification is needed. To that end recommend the afore noted proposed change and the following explanation.	The access to Grade A zone and Grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel. Companies should establish written procedures for the qualification of personnel commensurate with the assessed level of risk of their job function. These procedures should take into consideration requirements for training, cleanroom classification appropriate gowning/qualification, the level of supervision, and a demonstrated aseptic proficiency in the performance of aseptic process activities demonstrated 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. Where required, compliance with aseptic gowning procedures should be assessed and confirmed, periodically reassessed at least annually and should involve both visual and microbial assessment (using monitoring locations such as hands, arms, chest and forehead. Refer to paragraph 9.30 for the expected limits).	Section 7.5 represents an improvement over previous language. It contains important guidance and points for industry. However, during the PDA expert committee review, it became apparent that there remained significant points where clarification is needed. To that end recommend the afore noted proposed change and the following explanation: 1. The opening sentence of 7.5 refers to "access to the Grade A zone". This infers that cleanroom personnel are permitted to be present in the Grade A zone during aseptic operations. This is probably not the intent. To clarify intent, we recommend starting the paragraph with a reminder of the restriction. 2. Further in that sentence, there is a requirement for aseptic gowning training. However, those working in the Grade A zone of an isolator should not require aseptic gowning or relate training. To clarify intent, we recommend a note on where gowning is required. 3. Personnel not performing activities during the aseptic operation (e.g. off-shift cleaning/sanitization and maintenance performed prior to the sanitization of the cleanroom) should not be deemed as unqualified and require constant supervision, if they do not participate in an APS. There is no benefit nor is it feasible for these personnel to perform their non-aseptic processes during an APS. To clarify intent, we recommend the qualification be commensurate with the assessed level of risk of their job function. 4. We are concerned that the requirement for qualifying cleanroom personnel through participation in an APS will result in many ATMP companies having to interrupt production operations to accommodate additional long duration APS studies to qualify new cleanroom personnel. Because many of these operations occur in cleanrooms with multiple BSCs, this interruption will result in a reduction of output of needed medicines/therapies. In addition, waiting to schedule APS will reduce the ability to add cleanroom personnel. This will have a direct effect on output of these therapies. To avoid this unintended negative consequence, we recommend that alternative methods for cleanroom personnel qualification be allowed, as noted in the proposed change. 5. In general, we are concerned that the requirement for participation in the APS motivates companies to focus on the APS as the primary means to qualify personnel. Because the APS is not designed nor sensitive enough to demonstrate the qualification of cleanroom personnel, the primary use of APS for personnel qualification will divert efforts from more useful methods and provide inaccurate process confidence. To avoid this misconception, we recommend the replacement of the requirement for the APS with a requirement for demonstrating aseptic proficiency. This allows companies to continue to use the APS, if warranted, but adds the flexibility to develop and use more modern and effective cleanroom personnel qualification methods. 6. It is important to note that the proposed addition of "a demonstrated aseptic proficiency in the performance of aseptic process activities" in place of the requirement for "participation in a successful aseptic process simulation (APS)" is not designed to exclude the use of APS. Rather it is designed to allow companies the ability to design and use the most effective means to demonstrate aseptic process performance. Companies can certainly opt to use the APS, if they find that is valuable and appropriate.

851-853	As currently written, the section may be misinterpreted as requiring the qualification include a determination how long the garment can be worn.	Every operator entering Grade B or+C53:D54	The rewording of the last sentence clarifies that the intent of the section is that the qualification should be used to verify the maximum uses, washing cycles, and sterilizations, rather than time it can be worn.
973-977	As currently written, the section requires clarification to reinforce the proper determination and inclusion of duration in the aseptic process.	The duration of each aspects of aseptic preparation and processing should be established and defined by a method deemed appropriate by the CCS. The CCS should address the following; limited to a defined and validated maximum time including but not limited to: i. The holding times between equipment, component, and container cleaning, drying and sterilization. ii. The holding times for sterilized equipment, components, and containers before use and during filling/assembly. iii. The holding times for a decontaminated environment, such as the RABS and isolator before and during filling /assembly. iv. The time between the start of the preparation of a product and its sterilization or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process. There should be a maximum permissible time for each product that takes into account its composition and the prescribed method of storage. v. The holding time for sterilized product prior to filling. vi. The aseptic processing time. vii. The filling time. viii. The maximum exposure time of sterilized containers and closures in the critical processing zone (including filling) prior to closure.	There are three changes recommended to clarify the intent of the section. "Each" has been removed in the opening sentence, because the relevance of the duration of given aspect or activity of the aseptic process varies in importance according to that aspect or activity. Some durations should be defined and some not. Defining and maintaining durations that are not important may limit manufacturing output or efficiency. "Limited to a defined and validated maximum time" has been replaced with "established and defined by a method deemed appropriate by the CCS" in the opening sentence, because time is not validated, it is a process with an established time that is validated. Added explicit reference to the Contamination Control Strategy as the basis for the selection of the most appropriate approach to demonstrate the suitability of the mentioned hold times "Not limited to" have been added to the end of the first sentence to allow for inclusion of other aspects or activities not mentioned in the current text. Subsection viii has been removed, because it is covered by aseptic processing time in subsection vi. In addition, it would not be feasible to accurately determine a maximum exposure time for all sterilized components, because in theory given vials and stoppers may remain on a turntable or in a stopper bowl for the entire run.
1235-1237	As currently written, this section may be mis-interpreted as incorrectly indicating that the drain at the bottom of the chamber is always a coldspot where temperature recording is required. While this is may be correct for prevacuum sterilizers, this is not always case with superheated waterspray or water immersion sterilizers.	For autoclaves capable of performing prevacuum sterilization cycles fitted with a drain at the bottom of the chamber, the temperature should be recorded at the chamber drain this position throughout the sterilization period. For steam in place systems, the temperature should be recorded at condensate drain locations throughout the sterilization period.	Clarifications have been made to reinforce that the requirement for recording temperature at the drain is relevant to prevacuum cycle autoclaves. The drain at the bottom of the chamber for prevacuum sterilizers is the naturally occurring coldspot for this prevacuum sterilizers due to the design where air and condensate are controlled to pool in this location followed by subsequent removal from the sterilizer. A drain at the bottom of the chamber for other types of sterilizers may not always be the sterilizer coldspot and a true coldspot may not exist for certain sterilizer types. For example, superheated waterspray sterilizers operate with a specified level of water in the vessel and the outlet/drain at the bottom of the chamber is connected to a recirculation spray loop and this chamber outlet/drain may not be a sterilizer coldspot.

1239-1243	As currently written, the section does not clearly define critical processing parameters and equilibration time could be incorrectly interpreted to be included	Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature and maximum temperature range during exposure. Validation of fluid cycles should include temperature, time and/or Fo. These critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilization validation and routine cycle acceptance criteria, as applicable.	'As applicable' has been added to the end of the section, because equilibration time can only be calculated through the use of heat penetration probes in product which is not always the case with routine cycles.
1245-1247	As currently written, the example in the section may be misinterpreted as being a prescriptive and exclusive requirement.	Leak tests on the sterilizing system should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilization, to a pressure lower than the environment surrounding the sterilized system.	The example has been removed, because the specified weekly frequency for the leak test is excessively prescriptive. The frequency of the leak test and other sterilizer suitability tests should be based on QRM principles and tailored to each specific sterilizer. For example, a weekly frequency may not be necessary for modern well-maintained prevacuum sterilizers while a frequency greater than weekly could be necessary for older sterilizers.
1249-1253	As currently written, the section includes examples that are open to interpretation, require clarification to align with intent of the section, and may be limiting in application.	There should be For porous hard good loads and SIP cycles validation studies should provide adequate assurance of air removal prior to and during sterilization when the sterilization process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle on a frequency determined and justified through a risk assessment (normally performed on a daily basis) or an air detector system. Loads to be sterilized should be designed to support effective air removal and be free draining to prevent the build-up of condensate.	The examples have been removed and replaced with definitive sterilization circumstances and QRM based criteria, to prevent misinterpretation and improve clarity. The requirement of a daily air removal test is too prescriptive and constitutes an unnecessary burden for companies that utilize modern and properly maintained sterilizers and steam supply systems. Adequate air removal is demonstrated with the use of heat penetration probes in product during sterilization validation studies with correlation to critical process parameters. Since heat penetration probes in product and/or air detectors are not utilized in all routine cycles, the achievement of validated critical process parameters provides assurance of air removal. The specified daily frequency for the air removal test is excessively prescriptive. The frequency of the air removal test and other sterilizer suitability tests should be based on QRM principles and tailored to each specific sterilizer and steam supply system. For example, a daily frequency may be necessary for older systems while this frequency not be necessary for modern well-maintained system.

1260-1264	As currently written, the section contains an example that may be misinterpreted as being the prescribed or exclusive option for WFI wetting. In addition, the section may be interpreted as implying that a risk assessment should be used to demonstrate the acceptability levels of wetness and holding times, which could lead to a biased, predetermined outcome assessment.	If it is necessary to wet equipment or components using WFI (e.g. ultrafiltration membrane) prior to the sterilization process, then a risk-based assessment should be carried out to demonstrate the acceptable dryness level that will not impact the sterility of the equipment sterilized and the product sterility assurance level. the minimum amount of WFI should be applied (as per manufacturers recommendations). The hold time between the wetting phase and sterilization and the hold time between sterilization and use should be justified based on risk assessment and validated to demonstrate the absence of impact on the sterility of the equipment and on the product sterility assurance level.	The proposed change removes "ultrafiltration membrane" to avoid any unintended limitations in allowable technology, by the use of an example. The proposed changes also remove the language referring to using a risk assessment to demonstrate acceptable dryness in respect to sterility assurance, because as currently written the section may be misinterpreted as allowing companies to ONLY perform a risk assessment to justify sterility assurance risk. Instead, it would be more useful to have the reader focus on the key risk posed by wet materials, which is contamination growing during a prolonged hold time, and risk of re-contamination after sterilization for wet material, by setting the quantity of WFI to be used and the actual holding times confirmed trough a validation.
1271-1278	As currently written, the section includes examples that may be misinterpreted as being prescriptive and exclusive. In addition, as currently written the section can be mis-interpreted as requiring positive pressure of all systems regardless of environment it is in or if it is a sealed system.	Where steam in place systems are used (e.g. for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to assure all parts of the system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilized. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilized by steam in place it should remain integral and where design and operation requires, held under positive pressure prior to use.	The examples have been removed from the first sentence, because the use of the examples may be mis-interpreted as setting requirements that are not limit alternative or additional aspects of steam in place design or are not beneficial. In addition, "where design, location, and operation requires" has been added to the last sentence, because some processes may not require and some systems may not be designed to be held under positive pressure. Where no benefit is gained from a system held under positive pressure, there should be no requirement for positive pressure, as the requirement may add complexity or need for system redesign. In addition, it is not always technical possible to ensure that critical locations (monitoring locations) are representative with the slowest to heat locations in a SIP system. Often the slowest to heat locations are first identified in connection with initial and/or routine validation. In addition, A requirement to hold steam in place sterilized lyophilizer chambers is particularly non-beneficial, because process controls are already in place to confirm chamber integrity after steam sterilization. There is a leak test at deep vacuum which ensure the integrity of the chamber up to the start of the loading process. Here positive pressure would not be necessary prior to the start of production and once loading begins, positive pressure would not be feasible. In addition, language should allow flexibility for different systems, including single-use.

1286-1288	As currently written, this section focuses exclusively on the achievement of temperature in the load which is insufficient to ensure sterilization efficacy. Sterilization efficacy can only be ensured through the achievement of time and temperature and/or F0 in the load. Additionally, not all sterilizers contain true worst case temperature monitoring positions. In these cases, it is important to correlate the temperature and time from monitoring locations to the overall heat history of the product load.	For the qualification of superheated water sterilizers systems, it should be demonstrated that all parts of the load meet the minimum required time/temperature or minimum required F0 and that routine monitoring probes are located in positions correlated with the product load heat history or in worst case positions identified during the qualification process.	The section has been reworded to reinforce that the qualification of superheated water sterilizers requires demonstration that a minimum heat history (time at temperature or Physical Lethality/F0) is met for the product load. The achievement of a minimum temperature without an associated time of exposure is meaningless in the qualification of moist heat sterilization process efficacy. Not all moist heat sterilizers contain consistent and reproducible worst case positions/coldspots that can be utilized for routine probe monitoring and control locations. In these situations, monitoring and controlling probes are located in reference positions to which the product load heat history is correlated during the development and qualification of the moist heat sterilization process.
2021	As currently written, the section may be mis-interpreted to require that sleeves entering the critical space during a controlled intervention be immediately monitored for viable contamination.	Personnel gloves (and any part of the gown assessed to pose a risk to product sterility that may potentially have direct impact on the product sterility (e.g. the sleeves if these enter a critical zone) should be monitored for viable contamination after critical operations and on exit from the cleanroom. Other surfaces on the gown should be monitored on exit from the cleanroom at the end of an operation	The example of sleeves has been removed and QRM language has been modified and added to clarify that the intent of the section is not to require operator gowns monitored after interventions. This monitoring would require the operator to leave the clean room and re-gown prior to re-entry. Because removing the operator from aseptic processing activities is disruptive and not necessary for all interventions, including inherent interventions and many corrective interventions, the decision to do so should be risk based. In addition, the wording related to end of day gown monitoring has been clarified to be consistent with glove monitoring.

2035-2044	As currently written this section can be misinterpreted and promote over-reliance on aseptic process simulations as the primary or sole means to validate the aseptic process and various aspects surrounding the aseptic process.	Periodic verification of the effectiveness of the controls in place for aseptic processing should include a process simulation test using a sterile nutrient media and/or surrogate in place of the product. The process simulation should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to quality system and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient media and/or surrogate should be made based on the ability of the media and/or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process at all processing stages. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. sterile aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible can be developed and justified. Where surrogate materials, such as buffers, are used in parts of the process simulation, the surrogate material should not inhibit the growth of any potential contamination.	Sections 9.34 and 9.40 provide a good opportunity to improve aseptic process control by emphasizing failure prevention through process understanding, design and evaluation, rather than through detection and testing. In section 9.34, the first proposed change adds two sentences written to avoid the over-reliance on aseptic process simulations as the primary or sole means to validate the aseptic process and aspects of the aseptic process, including personnel performance, interventions, equipment suitability, product and material hold times, and environmental cleanliness. The sentences reinforce that while aseptic process simulations may be useful in uncovering weakness or under-addressed variables in the process, it is not sensitive enough to validate the performance of cleanroom personnel, the effect of personnel fatigue on the process, the effectiveness of controls, the effect of environmental exposure, or the design and condition of equipment. The sentences are added to dissuade companies from merely performing aseptic process simulations, rather than relying on more important means to ensure control of the aseptic process, including proper process design, contamination control strategy, training, and process understanding. This misunderstanding has led to over confidence in less than optimal processes and the acceptance of improper process activities. The second proposed change to section 9.34 adds risk assessment language in place of the word "all product characteristics". The change clarifies and emphasizes the need to take into consideration those characteristics of the product that pose a risk or have an effect on the performance of the aseptic process rather than all product characteristics, some of which have no impact on product sterility during the aseptic process. Companies should evaluate their products on a risk basis and make and be prepared to defend decisions in accordance with those assessments. Building on the points made in section 9.34, the examples in section 9.40 have been replaced with risk assessment language and the word "situations" has been added to reinforce the need for companies to evaluate and include any aspects of the process that pose a risk to product sterility, rather than only focus on the items listed in the example.
2162-2170	As currently written, the examples in the section may be misinterpreted as being prescriptive and exclusive. In addition, clarification is needed for the categorization of shifts and operators included in the APS. In addition, the performing APS tests before shutdowns may not be beneficial.	Process simulation tests should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services, equipment which are assessed to have an impact on the sterility assurance of the process and product sterility. or equipment (e.g. modification to the HVAC system, equipment, major facility shut down, changes to process, number of shifts and numbers of personnel etc.). Normally, process simulation tests (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each working shift. Each qualified operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.	Building on the points made in section 9.34, the examples in section 9.40 have been replaced with risk assessment language to reinforce the need for companies to evaluate and include any aspects of the process that pose a risk to product sterility, rather than only focus on the items listed in the example. The second proposed change in section 9.40 replaces "operator" with "qualified operator" and "shifts" with "working shifts" to clarify and align with other text in the Annex. The third proposed change to section 9.40 change eliminates the requirement for performing process simulations before a shut down or decommissioning. The change is meant to emphasize that companies should have contamination control strategies that provide confidence and assurance of product sterility for every batch and every day that the process is commercially performed, as mentioned in the proposed change to section 9.34. It is important that companies understand that confidence should be based on proper process and Quality System design, process performance, and training, rather than on passing a media fill. If the process and the control strategy have been properly designed, performed, and monitored, then there should be confidence that the product manufactured by that processhas maintained quality attributes up to the time the process is stopped. If that the process and control strategy do not provide that confidence, then the process inadequacies must be addressed before the process is performed. The passing of media fills does not replace that need. To the contrary, it will result in a false sense of confidence and dissuade companies from relying on prevention through proper process design and control, rather than a reliance on testing.

2209-2216	As currently written, the section may be misinterpreted as requiring complete visual inspection training and set-ups for people inspecting media filled units. In addition, as currently written, the section requires growth promotion tests (GPT) using local isolates, which may not be scientifically beneficial.	On completion of incubation: i. Filled APS units should be inspected by staff, who have been appropriately trained and qualified for the detection of microbiological contamination in the visual inspection procedures, under conditions similar to those for visual inspection., Inspection should be conducted under conditions that facilitate the identification of any microbial contamination. ii. Samples of these units should undergo positive control by inoculation with a suitable range of reference organisms. and local isolates	The wording in sub-section i addressing more general visual inspection training and conditions has been replaced with microbiological contamination related wording to clarify the intent of the sub-section. 'Local isolates' has been removed from sub-section ii, because the purpose of performing GPT following the incubation period of a media fill is not to demonstrate the media has acceptable growth promoting properties, which is established during incoming QC testing, but to demonstrate that the media has not been compromised during the preparation and sterilization (i.e. incorrect formulation, excessive heating, prolonged storage under unfavorable conditions, etc.) and there were no residual cleaning agents or product residues remaining in the system that could have mixed with the media and rendered it unfavorable for growth promotion during incubation. Locally recovered microbial environmental isolates (EI) are not standardized cultures that remain consistent and comparable between tests and laboratories. Unlike the QC microorganisms cited by the various compendia to be used for GPT and suitability testing. Once isolated and held as an EI culture in the microbiology laboratory any specific phenotypic traits could be lost or changed during its maintenance on a high nutrient media Supplemental information and references: The use of local microbiological isolates for performing post media fill incubation growth promotion testing is unsuitable based on the published scientific evidence listed below: • There is experimental proof to this observation. Adaptation of environmental bacteria to laboratory conditions can lead to modification of important traits, that has been termed domestication (1). These authors state that "four newly isolated strains of E. coli showed changes in metabolism, morphotype, and fitness", in addition, "the domestication changes are not uniform across a species or even within a single domestication population". The laboratory liquid or solid media environment during storage has also be documented during the domestication effects (1). • In research by Jan Steensels, et al.,2019, their report confirms the phenomena of "domestication of Industrial Microbes". They proved that during the domestication process, microbes gained the capacity to efficiently consume particular nutrients, cope with a multitude of industry-specific stress factors, often at the cost of a reduction in fitness in their original, natural environments. So, in time, during laboratory storage making them less representative of their original environments, which they are falsely designated to represent during the GPT (2). • Bacteria evolve rapidly not only by mutation and rapid multiplication, but also by transformation by naked DNA uptake and recombination but also with plasmid adsorption via the Gene-transfer processes under natural conditions. These acquired traits can be cured or lost during artificial laboratory sub-culturing when the selective pressures that induce their expression are no longer available. The loss of an EI unique plasmid during laboratory storage would render the isolate non- representative of the source environment (3). • Collaborating evidence was published by Bin Liu, et al.,2017 that demonstrated the effects on four strains of E. coli, that exhibited up to 25 mutations in all cultures of natural isolates within 10 days of transfer in rich media or with a single growth cycle involving an extended stationary phase (4). References 1. Gustavo Eydalllin, B. Ryall, R. Maharjan and T. Ferenci. (2014), "The nature of laboratory domestication changes in freshly isolated Escherichia coli strains", Environmental Microbiology 16(3), 813-828 2. Jan Steensels, B. Gallone, K. Voordeckers, and K. Verstrepen. (2019), "Domestication of Industrial Microbes," Current Biology 29, R381-R-393 3. Christopher Thomas and K Nielsen. (2005), "Mechanisms of, and barriers to, Horizontal Gene Transfer between Bacteria. Nature Reviews Microbiology 3, 711-721 4. Bin Liu, G. Eydallin, R Maharjan, l. Feng, L. Wang and T Ferenci. (2017), "Natural Escherichia coli isolates rapidly acquire genetic changes upon laboratory domestication", Microbiology, 163, 22-30
2.3. Other significant comments			
Overall	Throughout our comments to the Annex 1 revision, we have recommended the removal of specific examples. However, as a general recommendation, we urge the authors to consider removing the examples, where those examples may result in misinterpretation of intent of the Annex section.	Removal of examples.	Numerous sections throughout the 2020 revision version of Annex 1 cite or include examples. These examples which are noted in parentheses, or with the connotation of e.g., for example, such as, etc. Our members have reported that the use of examples may be and often are misinterpreted by the reader of the Annex and by some inspectors as the prescriptive or exclusive intent and expectation of the EMA. While we understand that this is not the intent of the Annex 1 authors, this misinterpretation can result in unintended negative consequences, including: … discouraging companies from considering or using new, innovative, and beneficial alternative approaches, because those approaches are not covered by or aligned with the provisions noted in the examples, … discouraging companies from using risk based decisions to develop new beneficial approaches, … companies opting to use approaches that may add unnecessary burden and take away resources needed to for more beneficial efforts, … companies adopting the example without adequate assessment, justification, validation to support the suitability of that values or way of working to their process, assuming instead that if they merely following the example will be sufficient for process control.

Overall	Both pyrogen and endotoxin are used throughout the 2020 revision, sometimes appearing to be used interchangeably and sometimes redundantly. While the words denote similar entities, they are not always interchangeable and may involve different control and detection methods. In many cases, the term pyrogen is encompassing, and where this is the case, we recommend sole use of that term.	Use of “pyrogens” and “endotoxin.”	It is important to recognize that not all potential pyrogens are bacterial endotoxins. Historically, parenteral product recalls due to non-endotoxin pyrogens have occurred (e.g. peptidoglycan contamination of dialysis solutions) and the potential for non-endotoxin pyrogen contamination remains a risk. Throughout the 2020 revision the terms pyrogen, pyrogens or pyrogenic are mentioned 18 times. The terms endotoxin and endotoxins are used nine times. For the most part the usage of the term pyrogen and in certain required sections the usage of the term endotoxins is appropriate, but there are a limited number of places where the verbiage can be simplified and maintain consistent use of the more scientifically correct term of pyrogen. To ensure consistency and fidelity to accurate science the term the decision on which term is more scientifically accurate should be made and justified as part of the CCS development. Specific references to these sections are noted as an appendix to our comments.
Overall	We continue to advocate for the replacement of traditional terms that may not be technically correct, with more scientifically accurate terms. To that end, we recommend that the authors use the opportunity for Annex 1 revision to educate the industry on the need to replace the phrase “non-viable particulates” with “total particulates”.	Use of “total particulates” rather than “non-viable.”	As discussed broadly at PDA workshops, conferences and meetings, 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.

Overall	The 2020 Annex 1 represents an improvement over the 2017 version in that it largely denotes Alert Levels, rather than Alert Limits, because Alert levels is a more constructive term. However, the continued use of Limits in general and Action Limits in particular, should be reconsidered and also replaced with Levels, as noted in the 2018 recommendations.	Use of "levels" rather than "limits"	Since 2018, the importance of the recommendation has been reinforced during PDA/industry workshops and conferences related to Annex 1 revision. These meetings showed that the industry was making progress in understanding the benefit of analyzing data and trends, rather than reacting to excursions from prescribed limits. This recognition of the importance of analysis of trends will allow companies to recognize problems before they reach a level of failure, thus improving process performance and reducing risk to product sterility. For this reason, we continue to advocate for the use of Levels rather than Limits. As stated in 2018, "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."
Overall	Where applicable, the guidance, recommendations and requirements presented in the Annex should be consistent with recognized ISO standards, such as those presented in the ISO 14644 series.	Cleanroom related topics should be consistent with ISO standard.	Throughout the 2020 Annex 1 revision, clean room design, classification, qualification, operation and monitoring are discussed. Where applicable, the guidance, recommendations and requirements presented in the Annex should be consistent with recognized ISO standards, such as those presented in the ISO 14644 series. This consistency is important, because it will reduce confusion and misinterpretation of the regulatory expectations regarding industry guidance, consensus standards, and stated regulatory requirements.
Overall	In some cases, the sections do not distinguish between different requirements for terminal sterilization and aseptic processing. Here the apparent lack of differentiation will lead to misapplication of control strategies where there may not be an intent or benefit, including conflicts addressing moist heat sterilization, sterility testing, and equipment sterilization.	Clear distinction should be made between requirements for aseptic processing and terminal sterilization.	Most of the sections in the Annex primarily apply to aseptic processing. While many of these sections are also applicable to terminal sterilization, several requirements are either not applicable, unnecessary, or not feasible when applied to terminal sterilization. Throughout the Annex we attempted to identify and offer recommendations. In these cases, it is important that clear distinctions are made between respective requirements.

520-528	As currently written, the section may be misinterpreted as requiring the rotation of disinfectants, thus requiring clarity on the criteria for the evaluation of the effectiveness of a disinfection program and the need to holistically assess all the parameters which contribute to it.	The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. Cleaning programs should effectively remove disinfectant residues. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action and their combined usage is effective against all bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection program and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use). Where monitoring results show that the disinfection programme is not effective an investigation should determine the reason (e.g. not adequate disinfection frequency or disinfectant mode of action or disinfectant application/concentration…) and corrective action should be implemented Cleaning programs should effectively remove disinfectant residues.	Language has been added to reinforce the importance of a well-planned and qualified disinfection programme. Language has been removed that indicates that the treatment must be effective against all bacteria and fungi (as this is not achievable), and that a rotation of disinfectant is necessary, in addition to the use of a sporicidal agent. "More than one type of disinfecting agent should be employed" appears to recommend or require the rotation of disinfectants with different antimicrobial agents. In addition, Ineffectiveness of the disinfection programme is not always due to the mode of action of the disinfectant, all factors need to be considered, including e.g. disinfectant concentration, disinfection frequency, etc Additional reference material: This 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; Vicky G. Kastbjerg, Lone Gram, International Journal of Food Microbiology 160 (2012) 11–15, Josè E. Matinez, Pharmaceutical Technology (Feb.2, 2009); 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; Vicky G. Kastbjerg, Lone Gram, International Journal of Food Microbiology 160 (2012) 11–15, Industrial disinfectants do not select for resistance in Listeria monocytogenes following long term exposure; Josè E. Matinez, Pharmaceutical Technology (Feb.2, 2009): The Rotation of Disinfectants Principle. True or False?; USP 40 NF 35, chapter <1072> Disinfectants and antiseptics; PDA Points to Consider for Aseptic Processing Part 2 (2016)
572-574	As currently written, the section may be mis-interpreted as pertaining to terminal sterilization as well as aseptic processing. In addition, as currently written, the section may be mis-interpreted as requiring the sterilization of equipment that contact surfaces on sterile components that do not contact sterile product, i.e. the exterior of vials. In addition, as currently written, the section can be interpreted as limiting sterilization to traditional methods that are not well suited for transfer of large equipment into isolators.	Direct and indirect contact parts used for aseptic processing should be sterilized. Direct contact parts are those that the sterile product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that come into contact with sterilized critical items and components the surface of critical items and components that contacts sterile product. Where indirect product contact equipment design does not allow for heat sterilization and installation, a risk assessment should address the use and control required for alternative methods to address product sterility.	"Used for aseptic processing" has been added to the first sentence to clarify that the requirement for sterilization pertains only to aseptic processing and not terminal sterilization. Sterilization of these parts is unnecessary and has not been a requirement for terminally sterilized parts products in the past. For this reason, it is recommended to relocate this section to Part 8 of the Annex 'Aseptic preparation and processing'. "Surface of" and "that contact sterile product" have been added to the second sentence to clarify that the intent of the section is not to require sterilization of conveyors and rails that contact the exterior of sterile containers. In addition, a sentence has been added to the end of the section to clarify an allowance for alternative sterilization methods or combinations of methods. This is important, because since the 2017 version of Annex 1 was proposed there have been concerns expressed to the PDA from members that the Annex should allow for the pre-assembly and in-place sterilization of large, component handling equipment. Our concern is that without such options, companies may be dissuaded from using innovative isolator designs that are more compact and less risky, or companies may try to use transfer techniques for large sterilized equipment, that are not well suited to these isolator designs. We recognize that in-place sterilization methods may be complex and if not performed correctly may not be effective. However, any sterilization method proposed by a company should be properly validated and if so, should be allowed.

588-592	Currently as written this section may potentially be too prescriptive and may not align with supplier recommendations or standard language for certain instrumentation.	Particle counters, including sampling tubing, should be qualified. The tubing length should be no greater than 1 meter with a minimum number of bends and bend radius should be greater than 15 cm. The parameters of the complete sampling system (including tubing length, diameter, radii, probe size, number of bends) should comply with the manufacturer's recommendation for the particle counter selected. Portable particle counters with a short length of sample tubing should be used for classification purpose. Isokinetic sampling heads should be used in unidirectional airflow systems A sampling probe should be selected to permit close to isokinetic sampling in areas with unidirectional flow and should be positioned as close as possible to sample air representative of the critical location.	The use of prescriptive values for the length and bend radius may hamper the use of different methods, needed to support new manufacturing technologies, or it may allow values that are not optimal. We recommend the user rely and follow the instrument manufacturer recommendations as per ISO 14664. This will not preclude the use of different parameters as the particle counter technology evolves.The wording in the last line in the section has been changed to aligned with ISO14644-1 language for particles ≥5µm but is still applicable for particles ≥0.5µm.
741-744	As currently written the section may be misinterpreted as promoting the use of the APS to validate the number of people allowed in the cleanroom.	Only the minimum number of personnel required should be present in cleanrooms. The number of operators required should be determined during process design. The maximum number of operators in cleanrooms once determined should be, documented and validated during activities such as initial qualification and aseptic process simulations, so as not to compromise sterility assurance. This is particularly important during aseptic processing.	Those using the guidance should understand that the impact of the presence and behavior of people in the cleanroom involve variables that cannot be validated as one would validate other process parameters. The APS is a test designed to uncover process weakness not identified or adequately addressed in process design. It along with cleanroom qualification tests are not sensitive enough to determine the acceptability or an acceptable number of people. As currently written, the section may be misinterpreted as doing such, thus promoting a false sense of confidence that dissuades other more effective efforts to design a process that minimizes the number of people required. In addition, the number of persons should be determined prior to the qualification or validation studies, rather than during the studies. The proposed changes clarify the intent of the guidance without removing the concern.
775-781	The section as currently written disqualifies all personnel who participated in any part of a failed APS.	There should be systems in place for disqualification of personnel from working in or unsupervised entry into cleanrooms based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring program and/or after participation in a failed APS, where the failure is attributed to that person's aseptic technique or behavior. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering Grade B cleanrooms or performing intervention into Grade A zone, this requalification should include consideration of participation in a successful APS.	Wording has been added to clarify that where an APS fails as a result of causes unrelated to the aseptic technique or behavior of a person, that person or persons should not be disqualified from working in the clean rooms. Notwithstanding, the disqualified person must still be allowed back into the cleanroom to participate in the "requalification" APS.

805-816	The section as currently written may be misinterpreted as requiring a procedure for in line testing of sterile gowns at time of use.	The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. When the type of clothing chosen needs to provide the operator protection from the product, it should not compromise the protection of the product from contamination. Garments should be visually checked for cleanliness and integrity immediately prior to gowning and prior to entry to the cleanroom. Gown integrity should also be checked upon exit. For sterilized or effectively decontaminated garments and eye coverings, particular attention should be taken to ensure they have been processed, are within their specified hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments (including eye coverings) should be replaced if damage is identified or at a set frequency that is determined during qualification studies. Damage to garments may not be identified by visual inspection alone, so the qualification should consider any necessary garment testing requirements. The qualification of garments should consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.	The proposed change rephrases the section to clarify that damage should be considered as part of the initial qualification of the garment, while making it clear that once qualified, visual inspection of the garments (as stated in the second sentence) is regarded as sufficient.
818-819	The section as currently written may be misinterpreted as encouraging excessive movement if cold and remaining in the cleanroom if sweating excessively. In addition, the prevention of shedding may not be feasible.	Clothing should be chosen to limit prevent shedding due to operators movement excessively (when cold) or sweating (when hot).	Cleanroom clothing is not airtight and therefore does not prevent shedding. Instead it limits shedding. Excessive movements when feeling cold or when sweating should be prevented in cleanrooms, because of excessive particles shedding.
879-886	Suggested removal of the requirement for the mandatory use of Grade C environment for all products that actively support microbial growth: a comprehensive risk assessment should be made that can lead to different and more suitable approaches to ensure the sterility of the terminally sterilized product.	Preparation of components and materials should be performed in at least a Grade D cleanroom in order to limit the risk of microbial, pyrogen and particulate contamination, so that the product is suitable for sterilization. Where the product is at a high or unusual risk of microbial contamination (e.g. the product actively supports microbial growth, the product must be held for long periods before filling or the product is not processed mostly in closed vessels), then preparation should be carried out in a Grade C environment. Preparation of ointments, creams, suspensions and emulsions should be carried out in a Grade C environment before terminal sterilization.	The contamination control strategy must be based on comprehensive QRM which takes into account all different elements that contribute to the sterility assurance of the process and sterility of the product. Just relying upon the cleanliness grade of the manufacturing environment may give an incorrect sense of security and prevent to address other equally important or even more important elements that contributes to the product sterility. For example, many aqueous drug formulations actively support the growth of microorganisms, but proper validation of the mix to sterilization time limit and processing mostly in closed vessels can be utilized to effectively mitigate this risk without the requirement of a Grade C environment. Specifically, with processing mostly in closed vessels, there is a very limited level of exposure of the product to the mixing room environment which also supports the use of a Grade D environment for this operation. The requirement for the use of a Grade C environment for all products that actively support microbial growth represents an unnecessary burden on industry and provides negligible mitigation of risks to the assurance of product sterility.

894-897	As currently written, the examples noted in the section may be misinterpreted as being the prescribed or exclusive conditions for a requirement that may not always be accurate or beneficial for those noted conditions.	Where the product is assessed to pose 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, then the product should be filled in a Grade A zone with at least a Grade C background.	The examples have been removed from the section and replaced with QRM based wording, because all of the highlighted examples listed for applicability of this item do not necessarily represent a high or unusual risk of microbial contamination that could impact the assurance of sterility for terminally sterilized products. Further, it can be demonstrated that a Grade C environment and associated microbiological control practices result in a level of product bioburden that represents a very low challenge when compared to the challenge level of the biological indicator utilized to develop and qualify a terminal moist heat sterilization process. The requirement for the use of a Grade C environment for any of the filling conditions stated represents an unnecessary burden on industry and provides negligible mitigation of risks to the assurance of product sterility.
1190-1192	As currently written, the example noted in the section may be misinterpreted as being the prescribed or exclusive method, thus limiting the use of modern or innovative technologies.	Each heat sterilization cycle should be recorded either electronically or by hardcopy, on equipment with suitable accuracy and precision. Monitoring and recording systems should be independent of the controlling system (e.g. by the use of duplex/double probes). or have safeguards and/or redundancy to detect a cycle not conforming to the validated cycle parameter requirements and abort or fail this cycle.	The example has been replaced with broader language, because the expectation of a modern sterilization process should be a Quality by Design (QbD) approach which identifies all parameters, phases, times, etc., that are critical to a successful sterilization cycle. The design of the system should have a control strategy such that alarms and controls are in place that detect and abort a cycle that does not meet the validated cycle. This enables the use of automation (digital plant) to identify a cycle not meeting the parameters versus manual review. Independent probes could be a way to confirm that the routine cycle is in conformance with the validated cycle but are not the only way to do this. Identifying a non-compliant cycle can be accomplished through multiple instruments interacting (temperature, pressure, liquid sensors in drains, etc) as well as comparisons of temperature and pressure against the saturated steam curves that ensure a successful cycle versus having double temperature probes. The proposed modification sets this QbD expectation to identify the parameters upfront and ensures that the proper safeguards are in place to detect and abort a cycle not meeting a valid cycle. If the change is not accepted, request at least the acknowledgement in the requirement that a QbD approach to accomplish this is possible to allow technology to support these processes as much of industry is working to leverage digital plant, AI and other advanced systems to move away from manual reviews of sterilization reports.
1194-1197	As currently written, the section may be misinterpreted as being applicable to all sterilization loads, while the requirement is relevant for porous hard goods only.	The position of the temperature probes used for controlling and/or recording should be determined during and set prior to the validation which should include heat distribution and penetration studies and, where applicable, also checked against a second independent temperature probe located at the same position.	"During" have been replaced with "set prior to" to clarify that key process operating parameters including the positioning of monitoring probes should be known and in place for the validation study, rather than determined as a variable during the study.
1199-1203	As currently written, the section may be misinterpreted as being applicable to all sterilization loads, while the requirement is relevant for porous hard goods only.	For porous hard goods loads, Ssufficient time should be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period starts. For sterilization cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring the load probe temperature is controlled within defined temperature range prior to cycle commencement.	'For porous hard goods loads' has been added to the beginning of the section to clarify intent of the section. The requirement for the whole of the load to reach the required temperature before initiation of the sterilizing time period represents a requirement for load equilibration which is only applicable to porous hard goods loads. With liquid loads, solution formulations may include product fill volumes of up to 6 liters which results in a considerable lag in temperature of the load behind the temperature in the sterilizer. Therefore, temperature equilibration prior to the start of the sterilizing phase is not applicable for liquid loads as long as it has been demonstrated that minimum physical (F0) and biological lethality requirements for the sterilization process are reliably met.

1292-1296	Although recognized as separate processes, a currently written, section 8.66 does not separate the requirements for dry heat sterilization and depyrogenation.	Dry heat sterilization utilizes high temperatures of air or gas to sterilize a product or article. is of particular use in the removal of thermally robust contaminants such as pyrogens and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components and equipment are exposed should produce an adequate and reproducible level of lethality and/or pyrogen (endotoxin) inactivation/removal when operated routinely within the established limits. Dry heat sterilization is often combined with of particular use in the thermal removal of difficult-to-eliminate thermally robust contaminants such as pyrogens and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components and/or equipment are exposed should produce an adequate and reproducible level of lethality and/or pyrogen (endotoxin) inactivation/removal when operated routinely within the established limits.	The proposed changes to sections 8.66 clarify the intent of the section by separating the requirements for sterilization and depyrogenation into two sets of sentences.
1298-1306	As currently written, section 8.67 can be mis-interpreted as requiring that air flow visualization studies be carried out in the dry heat/depyrogenation tunnel.	Dry heat sterilization/depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the Grade A sterilizing zone by maintaining pressure differentials and airflow through the tunnel from the higher grade area to the lower grade area. Airflow patterns should be visualized and correlated with temperature studies. The impact of any airflow change should be assessed to ensure the heating profile is maintained. All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests should be performed to demonstrate air filter integrity (at least biannually) at a frequency determined by QRM. Any tunnel parts that come into contact with sterilized components should be appropriately sterilized or disinfected. Critical process parameters that should be considered during validation and/or routine processing should include, but may not be limited to:	The changes to section 8.67 clarify the intent of the section. Airflow visualization cannot be carried out in dry heat sterilization/depyrogenation tunnels. HEPA filter integrity testing should be based on QRM, taking into consideration monitoring (e.g. particulate count) and performance data, as well as the different working environment / aging for the hot and cold zones, and the filter replacement plan. Airflow visualization through or at inlets and outlet of dry heat sterilization/depyrogenation tunnels will provide no value beyond pressure differential and/or airflow velocity measurements.
1318-1320	As currently written, the section does not acknowledge that the depyrogenation is a combination of processes. In addition, as currently written, the section does not reinforce that if depyrogenation conditions are met, it is not necessary to prove sterilization.	When a thermal process is used as part of the depyrogenation process is used for any component or product contact equipment, validation studies should be performed to demonstrate that the process provides a suitable Fh value and results in a minimum 3 log reduction in endotoxins concentration. When this is attained, there is no additional requirement to demonstrate sterilization in these cases.	The first sentence has been changed to acknowledge that the depyrogenation process is a combination of washing/rinsing and thermal processes. It is important to recognize the role the non-thermal aspects play in the overall depyrogenation process. In addition, a sentence has been added to the end of the section to reinforce that where depyrogenation conditions are met, it is unnecessary to prove that sterilization conditions have been met, because the conditions for depyrogenation significantly exceed those for sterilization. Without this addition, the section may be mis-interpreted as requiring additional and unnecessary validation studies.

1327-1346	As currently written, the section should be clarified that not all the critical process parameters listed are applicable in case of hermetically packed loads.	Dry heat ovens are typically employed to sterilize or depyrogenate primary packaging components, finished materials or active substances but may be used for other processes. If the load is not hermetically packed, then the oven they should be maintained at a positive pressure relative to lower grade areas throughout the sterilization and post sterilization hold process. All air entering the oven should pass through a sterilizing filter. Critical process parameters that should be considered in qualification and/or routine processing should include, but may not be limited to: i. Temperature. ii. Exposure period/time. iii. Chamber pressure (for maintenance of over pressure) - if applicable iv. Airflow velocity speed - if applicable. v. Air quality within the oven - if applicable vi. Heat penetration of material/article (slow to heat spots). vii. Heat distribution/uniformity.	For hermetically packed loads, such as used in API sterilization, the requirement to have a positive pressure during sterilization and during the cooling phase would not be necessary, due to the product protection by the packaging barrier. As a consequence, requirements iii), iv) and v) are only valid as critical process parameters in certain other applications
1356-1357	The section as currently written would have the unintended consequence of excluding the use of ultraviolet irradiation as a method or part of a method.	Sterilization by radiation is used mainly for the sterilization of heat sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilization.	Sentence on UV irradiation as a not acceptable sterilization method has been removed, because while we agree that the current ultraviolet irradiation technology may not currently be an effective method for sterilization, improvements to the technology may make it a useful a suitable sterilization modality in the future.
1377-1379	As currently written, the section may be mis-interpreted as requiring BU monitoring for parametrically released EtO cycles	Unless parametric release has been approved, each sterilization cycle should be monitored with suitable BIs, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst case during validation.	The requirement for the use of BI's in this section precludes the use of the state-of-the-art practice of parametric release. Therefore, wording has been added to the section to clarify that EtO cycles can be properly controlled via parametric control, based on technology, i.e. without BIs, as per ISO11135:2014+A1:2019 Sections 11.1, D.9.5.5, D.10.5. and D.11.1. which permit the release of EO-sterilized product without the use of BI's.
1537-1538	As currently written, the section requires clarification for redundant filtration.	Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration set-up. In cases where a redundant filtration set-up is used, it should be taken prior to the first filter. Systems for taking samples should be designed so as not to introduce contamination.	Wording has been added to the section to address redundant filtration. In redundant filtration, each filter is validated to obtain a sterile filtrate, therefore the filtrate side of filter one should not be compromised. To determine the maximum allowable bioburden in front of the filtration system, the sample has to be taken in front of filter one, as the bioburden in front of filter two should be zero.

1609-1613	As currently written, the section may present requirements that cannot be met with existing equipment design.	For shuttle type equipment used for aseptic filling, the area between parison cutting and mould sealing should be supplied with Grade A air quality to protect this should be covered by a flow of filtered air to provide Grade A conditions at the critical zone. The equipment should be installed in at least a Grade C environment, provided that Grade A/B clothing is used. The filling environment should meet Grade A for viable and non-viable limits at rest and the viable limit only when in operation.	Grade A 'conditions' has been replaced with Grad A 'air supply', because it may not be feasible to demonstrate Grade A conditions at an active BFS shuttle parison cutting zone. The language inserted is consistent with similar challenges posed by capping systems as noted in section 8.25 and should be adequate for contamination control.
1630-1635	As currently written, the section requires that the capability of the extrusion system to be validated to a level that may not be attainable.	External particulate and microbial contamination of the polymer should be prevented by appropriate design, control, and maintenance of the polymer storage, sampling and distribution systems. The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be fully understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxins levels of the raw polymer should be defined and controlled within the CCS.	"Fully" has been removed from the opening sentence, because it is an absolute term, and while a good objective, would be impossible to demonstrate in relation to sterility assurance. The extruder system heats, mixes, and dispenses semi-moltant plastic resin. Its effect on sterility assurance relates to the exposure of the resin to lethal conditions during the extrusion process. However, because it is not possible to predict which resin is exposed to heat for a given length of time, it may not be feasible to validate time and temperature exposure to the extent traditional expected for heat sterilization.
1641-1643	As currently written, the section may be mis-interpreted as requiring process validation studies be conducted for any change, regardless of the outcome of the risk assessment.	The moulds used to form containers are considered critical equipment and any changes or modification to moulds should result in an assessment of finished product container integrity and should be supported by validation based on the outcome of that assessment.	Risk based wording has been added to the end of the section to reinforce that some changes, for example changes to engraved wording, would not necessarily pose a risk to product container integrity and would not require validation.
1711-1715	As currently written, the section refers to intrinsic aseptic connectors, when intrinsic sterile connectors would be more accurate.	It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing / pipework) to the sterilized product pathway after the final sterilizing filter should be designed to be connected aseptically (e.g. by intrinsic aseptic sterile connectors or fusion systems).	'Aseptic' is replaced with 'sterile' in the example, because the section refers to connections that may involve closed systems as well as aseptic connections. In general, "intrinsic sterile connectors" should be used consistently throughout the Annex for the purpose of connection of sterile equipment, including where used in Section 8.11. Line 936. Table 5. And Section 8.127. Line 1782.

1763-1765	The section as written may be misinterpreted as requiring testing of each SUS unit upon receipt and prior to use.	Assessment of suppliers of disposable systems including sterilization is critical to the selection and use of these systems. For sterile SUS, verification of sterility should be performed as part of the supplier qualification and on receipt and use of each unit.	Some points are already covered under 8.128 The reference to receipt and use of each unit has been removed. Because these tests add stress and may be destructive, a misinterpretation of the intent of this section could have unintended negative consequences. The removed text is not necessary, because Section 8.128, as currently written, already addresses the key requirements for SUS inspection. Reference 8.128 Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the products and its processes. On receipt, each piece of SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (e.g. appearance of exterior carton, product pouches), label printing, and review of attached documents (e.g. certificate of conformance and proof of sterilization) should be carried out and documented prior to use.
1875-1876	As currently written the section may be misinterpreted as requiring EM data from less or non-critical areas be reviewed for batch release.	Relevant results from environmental monitoring should be considered when reviewing batch documentation for finished product batch certification.	EM data from critical grades, class A and B, should be reviewed and considered before batch certification, but review of EM data from less critical grades e.g. class D should not uphold the batch certification, unless incidents raise a need for evaluate the data from lower grades. Review of data should be QRM based. With satisfactory result from the evaluation of EM data from class A and B there should be no need for including review of data from less critical areas as part of the batch certification. On the other hand, if challenges are seen in the grade A and B EM results in relation to release of a batch then it might be relevant to also evaluate the results from lower grades.
1956-1960	As currently written, the section may be misinterpreted as exclusively requiring those methods mentioned in the examples.	Where aseptic operations are performed, the frequency, selection and combination of methods should be QRM based and include methods for surface, air, glove, and gown monitoring, as noted in Section 9.30 microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on Grade A and B airflow patterns.	The examples have been removed from the section and replaced with QRM based language linked to section 9.30, because as currently written, the use of examples may be mis-interpreted as setting prescriptive requirements. This could lead to a perceived requirement that methods such as settling plates must be used in all isolators, including gloveless and robotic systems, where the changing of plates involves intrusive interventions that are detrimental to sterility assurance and may dissuade companies from using these and other more advanced technologies in the future. The proposed changes reduce the risk of this unintended consequence, without changing the intent of the section.
1974-1979	As currently written, the section may be misinterpreted as requiring for duration monitoring of Grade B areas.	Continuous viable air monitoring in the Grade A zone (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing including equipment (aseptic set-up) assembly and filling operations. The approach to monitoring of Grade B cleanrooms should be determined based on the risk of impact on the aseptic processing and to contamination of the product. The monitoring should be performed based on the determination of risk of aseptic processing including, but not limited to, inherent and corrective interventions, transient events, system deterioration, and risks caused by the interventions of the monitoring operations. The monitoring plan for Grade A and Grade B cleanrooms should be justified in the CCS.	The reference to Grade B areas has been replaced with QRM based language, because monitoring for the Grade B cleanroom should be determined using a QRM approach based on the overall risk to aseptic processing and to the product. The monitoring plan should consider all aseptic processing related risks including (should be provided as examples but not necessarily an exhaustive or comprehensive list) the interventions, transient events, causes of system deterioration, and risks inherent to the monitoring operations employed.

1986-1988	As currently written, this section could be mis-interpreted as requiring companies qualify the overall recovery efficiency for settle plates, viable active air and surface monitoring by the user.	Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. The recovery efficiency of the sampling methods chosen should be qualified to confirm that sanitizing agents do not influence the recovery of microorganism.	For viable air sampling these qualification studies are difficult to execute based on several reasons, including standardization of recovery studies and Biosafety regulations for the microbiology laboratory. The proposed change is aligned with the requirements stated in Eudralex Annex 15: Qualification and Validation: 9.3, and clarifies the intent of the section as focusing on the effect of sanitizing agents. Reference: Eudralex Annex 15: Qualification and Validation: 9.3. Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test to confirm that sanitizing agents do not influence the recovery of microorganism.
1990-2008	As currently written, the section uses the term Action Limit, when Action Level would be more effective. In addition, as currently written, the suggested types of monitoring data reporting may be mis-interpreted as the only prescribed reporting format, thus limiting the use of existing or future alternative methods. In addition, as currently written, the section can be mis-interpreted to require that gown monitoring results exhibit no growth.	Action limits levels for viable particle contamination are shown in Table 7 <image> a. Settle plates should be exposed for the duration of operations and changed as required after 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used). Individual settle plates may be exposed for less than 4 hours. b. It should be noted that for Grade A, any growth should result in an investigation. However, certain alternative methods are not be growth based and may be reported as 0 cfu, no detection, or in another format. c. Contact plate limits apply to equipment and clean room and gown surfaces within the Grade A zone and Grade B area. Maximum gown monitoring levels should be defined and justified based on assessed risk posed to product sterility. Routine gown monitoring is not normally required for Grade C and D areas, depending on their function.	"Action limits" has been changed to "Action levels", because levels denote an analysis of trends, providing useful information to make informed, sound risk-based decisions, as we believe is the overall intent of the section. Limits denotes an absolute threshold that may never be crossed, not allowing for such risk-based decision making. Action levels should be risk based, accounting for cleanroom/process design, technology employed, and historical study results. In addition, a note has been added to address the manner in which data be reported to allow for alternative methods, where data cannot be reported in terms of growth In addition, gown monitoring has been separated from equipment and clean room surface monitoring, because it is impractical, unlikely, and unnecessary for gown results to be maintained as no growth or zero after gowned personnel have been in the clean room for a length of time.
2014-2019	As currently written, the section may not allow for the use fo rapid microbiological methods that do not allow for species level identification.	Microorganisms detected in Grade A zone and Grade B area should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in Grade C and D areas (for example where action limits or alert levels are exceeded or where atypical or potentially objectionable microorganisms are recovered). The approach to organism identification and investigation should be documented. Where alternative rapid microbiology or other methods are used, which do not allow for speciation, the justification for using such methods should be made based on the benefit of these methods compared to the risk posed by limited identification capability.	QRM based language has been added to the end of the section to allow for alternative, rapid methods that might not provide species level identification. In this case, it may be more importance to be able to act fast on a hit rather than being able to do the identification. RMM gives the possibility of acting fast on a hit, which might be of higher importance than being able to do the identification

2046-2085	As currently written, the sub-sections i, iv, and vii require clarification of terms to more accurately reflect the intent of the section. Also - as currently written, subsections vi and vii may be misinterpreted as requiring a full cycle APS duration.	i. Process simulation tests should assess all aseptic operations performed subsequent to the sterilization and disinfection decontamination cycles of materials utilised in the process to the point where the container is sealed. iv, Process requiring the addition of sterile powders should use an acceptable surrogate material in containers similar to those used in the process under evaluation. the addition of sterile powders should use an acceptable surrogate material in containers identical to those used in the process under evaluation. vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain including filing, transport, loading, a representative portion of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters. vii. The lyophilization process simulation should mimic duplicate all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling-over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable: • The use of air to break vacuum instead of nitrogen. • Replicating the maximum interval between sterilization of the lyophilizer and its use. • Replicating the maximum period of time between sterilization and lyophilization. • Quantitative aspects of worst case situations, e.g. loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.	'Decontamination cycle' has been replaced with 'disinfection' in sub-section i, because materials entering the critical zone are disinfected. Sub-section iv. has been modified to replace the difficult to interpret "acceptable …" with risk based language for selection of surrogate materials and container. 'Identical' has been replaced with 'similar' in subsection iv, because it would impractical to demonstrate that containers are identical. 'Duplicate' has been replaced with 'mimic', in subsection vii, because it would be impractical to demonstrate that all aspects of the process have been duplicated exactly. 'A representative portion of' has been added to 'chamber dwell' and the reference to replication of maximum time between sterilization and lyophilization has been removed in sub-section vi, because an APS duration of the entire cycle dwell could be multiple days, and this would be impractical and unnecessary. The third bullet point under sub-section vii. has been deleted, because it presents a requirement that may be impractical and unnecessary. The frequency for sterilization is correlated to the actual risk of chamber contamination (eg during loading) as per point 8.111 and 8.112, and a sterilization process may be not necessary for each cycle for Lyophilizers loaded by automated closed systems or located within systems that exclude operator intervention – thus it would be impractical to simulate such period of time (with intermediate lyophilization cycles) and not necessary provided that the sterile chamber is protected from the external environment .
2090-2095	As currently written, the frequency of intervention inclusion is open to interpretation and misinterpretation.	i. Inherent and corrective interventions representative of the routine process performed in a manner similar to the manner in which they are performed during the routine aseptic process. at the maximum accepted frequency per number of filled units (e.g. loading of vials into a lyophilizer). ii. The inclusion and frequency of interventions in the APS should be based on assessed risk posed to product sterility. iii. Corrective interventions, that occur frequently during routine production, in a representative number and with the highest degree of acceptable intrusion (e.g. correcting jammed stoppers).	The language in the section has been revised to clarify the intent of the APS, because we understand, the intent of the APS is not to validate interventions or to show that a given frequency of interventions is acceptable. The inclusion of interventions in the APS is important because interventions are a part of the aseptic process that is being simulated. However, the APS is not sensitive enough to confirm or establish the acceptability of interventions. Instead, interventions are acceptable based on the design of the process in respect to first air and product exposure and the training of the people performing those interventions. Repeating interventions does not increase the risk of failure, nor the chances of uncovering an improperly designed or performed intervention. Interventions are proper or not. Therefore, the number of times an intervention is repeated during an APS does not establish an acceptable limit for the frequency of that intervention. For inherent interventions, the correct number and frequency performed during the APS should be whatever the frequency is to maintain normal product rates during the period of the APS. For corrective interventions, the frequency should be assessed based on the value of the scientific information obtained from repeating the performance of the intervention.

2117-2138	The three subsections have been changed to clarify the intent for each section and reduce the risk of misinterpretation.	iv. Maximum permitted holding times for sterile product and associated sterile components and equipment exposed during the aseptic process. v. The method of detection of microbial contamination should be scientifically justified. to ensure that any contamination is detectable. ix. Where the manufacturer operates different or extended shifts, then the APS should be designed to capture specific factors specific to those shifts that are assessed to pose a risk to product sterility. (e.g. for those manufacturing during a night or extended shift, fatigue should be considered). Because it is not possible to simulate human fatigue during an APS, where human fatigue is assessed to pose a risk to product sterility, the process should be modified or designed to reduce the impact or risk of such fatigue.	In subsection iv, the reference to sterile components has been removed, because there would be not be practical to try to estimate or demonstrate the amount of time that individual vials would stay on a turntable or individual stoppers would stay in a bowl or hopper. In theory, one or more of these components could be exposed for the entire production run or for a very small part of the run. In subsection v., the reference to ensuring that any contamination is detectable has been removed, because it is not possible to ensure that all or any contamination present in the clean room will be detected using standard media fills. In subsection ix., the reference to including fatigue as a factor in the APS has been removed and replaced with wording promoting a risk based approach, because, as understood, (1) it is not possible to simulate fatigue in an APS and (2) it is not always the case that night shift personnel would be any more susceptible to fatigue than day shift. However, where fatigue is judged to pose a significant risk, the process should be modified or designed to minimize the impact or risk of fatigue.
2172-2175	As currently written, the section may be mis-interpreted as requiring performance of multiple APS tests for manual operations that are not filling and stoppering, which would be overly restrictive and burdensome for ATMP manufacturing.	Where manual operation filling and/or stoppering occurs, each type of container, container closure and equipment train should be initially performed validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each shift. Where manual connections and manipulations occur, clean room personnel performing those operations should be qualified in those operations and the APS for the process should be performed according to the guidance in the preceding sections. The APS batch size should mimic that used in the routine aseptic manufacturing process.	'Manual operation' has been replace with 'manual filling and/or stoppering' to clarify the intent of the section. In addition, 'validated' has been replaced with 'performed' to clarify that the APS does not validate the process or aspects of the process. A sentence focusing on manual connections and manipulations, other than filling and stoppering has been added to clarify the intent of the section. It is difficult to interpret this section and intended requirements without understanding the context and scope of "manual operations" as it relates to the operations covered by Annex 1. For instance, the requirements for the manufacture of sterile ATMPs, which may include many manual operations, does not include similar requirements (per EudraLex Volume 4 Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products). Explicit verbiage required for what is required by "each type of container, container closure, and equipment train". "Each type" may be interpreted as the acceptable use of a family (for multiple equipment trains or workstations) or a matrix/bracketed (container and closures) approach may be applied for the purposes of APS? Note that this section also requires revalidation "with one APS approximately every 6 months" which is inconsistent with the requirement in the preceding Section 9.40 that states "Normally, process simulation tests (periodic revalidation) should be repeated twice a year (approximately every six months)…"
2353	As currently written, the definition implies that and can be mis-interpreted as the capability of the aseptic process is determined or caused through APS testing. Determination of capability through process design, rather than testing is a key principle of process control that is well articulated or implied in Annex 1, Annex 15, and ICH Q7 though ICH Q12.	Aseptic Process Simulation (APS) – A simulation of the entire aseptic formulation and filling process in order to determine verify the capability of the process to assure product sterility.	"Determine" has been replaced with "verify" to clarify the intent of the definition and align with the correct statement made in section 9.34, as well as its usage elsewhere throughout the Annex.

NEW	The term “campaign” is used throughout Annex 1, however there currently is no definition for the term.	Campaign – The manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to accepted control measures before transfer to another product. The products are not run at the same time but may be run on the same equipment.	The definition for campaign is based on that defined for “campaigned manufacture” from the PIC/S Guide to GMP for Medicinal Products Annex 2 glossary, as this term is used in same the context as that within Annex 1.
2393	Placing the definition in the glossary allows for reader to have useful access for definition and reference.	Cleanroom classification – A method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the non-viable airborne particulate concentration according to the method defined in ISO Standard 14644-1. i. “At rest” state – The condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as specified and standing by for operation, without personnel in the room. ii. “In operation” state – The condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode with the maximum number of personnel present performing or simulating routine operational work. In operation classification may be performed during simulated operations or during aseptic process simulations (where worst case simulation is required).	ISO 14644-1 is the consensus international standard for clean rooms and controlled environments and is referenced in Sec. 4.28. The Standard provides a consistent and universally accepted method for clean room classification and should be employed consistently across all regulated sites. Citing ISO Standard 14644-1 will help prevent misinterpretation of the intent of the Annex. Added the definitions for both “at rest” and “in operation” states as also shown in Section 4.31.
2400	The definition requires clarification related to its use with SIP and SUS applications.	Closed system - A system in which the sterile product is not exposed to the surrounding environment. For example, this can be achieved by the use of bulk products holders (such as tanks or bags) that are connected to each other by pipes or tubes as a system, with the system being sterilized after the connections are made. Examples of these can be (but are not limited to) large scale stainless steel reusable systems, such as those seen in active substance manufacturing, or disposable single-use bag and manifold systems, such as those seen in the manufacture of biological products. Closed systems, when used in this document, does not refer to systems such as RABS or isolator systems which are referred to as Barrier Technologies.	The example sentences describe also the connection of systems or process equipment with tubing, which typically describes a single-use process system. Such systems are not sterilized after connection, as these are gamma irradiated, pre-sterilized unit operations. Therefore, we suggest deleting the last part of the sentence. We added clarity with “stainless-steel” to the reusable system and changed “disposable” to “single-use”, as single-use is the global term used.

2414	As currently written, the definition can be enhanced with additional clarification. Contamination is defined as microbiological, chemical, or particulate contamination. A distinction should be made for microbiological contamination.	Contamination – The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens) often referred to as bio-contamination/ bioburden or of foreign particulate matter, into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.	"Bio-decontamination" has been inserted in the definition to distinguish and reinforce a terms often used in industry.
2449	As currently written, the definition may be misinterpreted as requiring that any and all contaminants be eliminated through decontamination. In addition, a distinction for microbiological contaminants should be reinforced to clarify the use of the definition throughout the Annex.	Decontamination – The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganism) to a predetermined level from an area, object, or person. The method for decontamination used (e.g. cleaning, disinfection, sterilization) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated. Decontamination of contaminants from microorganisms or the by-product of microorganism activity is often referred to as bio-decontamination. Unless otherwise noted, contamination used in the Annex implies bio-contamination.	"Any" has been removed and replaced with 'to a predetermined level', because it would not be feasible to achieve or demonstrate that any or all contaminants have been addressed in the decontamination process. In addition, a sentence has been added to reinforce that decontamination as used throughout the Annex primarily refers to the decontamination of microbiological contaminants. It is important to state and make that distinction to avoid misinterpretation of the intent of the Annex's recommendations and requirements.
2494	Sterile and aseptic are used interchangeably throughout the document and therefore both terms require to be listed in the glossary.	Intrinsic Sterile / Aseptic Connection device –Either a gamma sterilized single-use aseptic connector or a tube sealer.	The former glossary definition did not describe the typical sterile/aseptic connection detailed enough to be recognized as the gamma sterilized single-use connection. It could have been misinterpreted as the stainless-steel sanitary flange to sanitary flange connection.

2497	As currently written may be too prescriptive, we would suggest removing the example of (± 20 percent) as it may be misleading.	Isokinetic sampling head – A sampling head designed to disturb the air as little as possible so that the same particulates go into the nozzle as would have passed the area if the nozzle had it not been there i.e. the sampling condition in which the mean velocity of the air entering the sample probe inlet is nearly the same (± 20 percent) as the mean velocity of the airflow at that locations.	The description of "….. the mean velocity of the air entering the sample probe inlet is nearly the same (± 20 percent) as the mean velocity of the airflow at that location…." can give an unnecessarily strict interpretation by inspectors.
2502	The definition requires additional wording to reinforce its practical usage by industry.	Isolator – A contained, decontaminated environment meeting Grade A (ISO 5) conditions used for aseptic process manufacturing that provides an uncompromised, continuous isolation of its interior from the external environment. Once decontaminated by a validated cycle, an isolator prevents the microbiological contamination of sterile products and product contact surfaces of the interior by rigid wall enclosures and the supply of continuous, controlled overpressure of HEPA-filtered air.	The revised definition is aligned with a PDA definition that is linked to the practical usage of isolators in the industry and helps the reader understand the important aspects of the isolator.
2526	Current definition requires modification to distinguish processes that are used to fill product from processes that are used to prepare or manipulate sterile product.	Manual aseptic filling – An aseptic filling process where the operator manually places, fills, and /or seals an open container with sterile product. intervention is required to complete the filling of each container (e.g., as occurs during aseptic compounding operations). Manual aseptic operation – An aseptic process where operator manually performs activities on or to an open container, bag, or unit that contains sterile product.	Manual aseptic filling usually refers to the filling of small quantities of product, where semi-automated lines are not suitable. While manual operations may include other aseptic manipulations performed for ATMPS and other process, such as connections, mixing, pipetting, heat sealing, etc. Separate definitions are needed, because the controls required for filling and operations are different. "Manual operations" are identified in Section 9.41 with the examples provided of "aseptic compounding or filling". Manual processes are also identified in other sections of the Annex, e.g., Section 8.122.iii. refers to "The increase in the number and complexity of manual operations" and Section 8.129 which refers to "critical manual handling operations". The glossary currently only defines the specific term "manual filling" which is not inclusive of other manual aseptic processes or operations that may be performed.