



**PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME**

PI 058-1
28 October 2026

RECOMMENDATION

**INTERPRETATION OF THE MOST
IMPORTANT CHANGES IN THE ANNEX 1
ON THE MANUFACTURE OF STERILE
PRODUCTS (2022)**

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1. DOCUMENT HISTORY

- 1.1 Annex 1 to the PIC/S GMP Guide (PE 009) on the manufacture of sterile medicinal products (hereinafter referred to as GMP Annex 1) has been revised to reflect changes in regulatory and manufacturing environments, and provide clarification on how manufacturers can take advantage of new possibilities deriving from the application of an enhanced process understanding by using innovative tools as described in the ICH Q9 and Q10 guidelines. The new version of the Annex has been adopted in 2022.
- 1.2 Adoption of the new version of Annex 1 stipulated the revision of the “Interpretation document”, adopted by PIC/S as PI 032-2 in January 2010. The new interpretation document in the form of Questions & Answers was initially drafted by Switzerland / Swissmedic in 2023 and this document served as the starting point for work of the PIC/S – EMA – WHO Joint Implementation Working Group on the revised Annex 1 (A1IWG).
- 1.3 The draft prepared by the Working Group was reviewed by PIC/S members, EMA IWG and WHO before its final adoption. It was agreed that the technical interpretation of GMP Annex 1 should be the same between PIC/S, the EU and WHO.

Adoption by the PIC/S Committee	16 October 2026
Entry into force of version PI 058-1	28 October 2026

2. INTRODUCTION

2.1 Purpose and scope

- 2.1.1 In order to assure a harmonised conduct of inspections, with respect to the 2022 revision of GMP Annex 1, this document provides answers to key questions related to the changes in Annex 1 raised during the revision process and after implementation of the new version. This document reflects the most important changes, nevertheless it is not meant to address all changes within the Revision.
- 2.1.2 Purpose of this document is not to introduce any new GMP requirements.

2.2 Basics

- 2.2.1 The Revised Annex 1 to the PIC/S GMP Guide (PE 009), about manufacture of sterile medicinal products, was adopted on 9 September 2022 by the PIC/S Committee and came into force on 25 August 2023 (with the exception of point 8.123, which became binding from 25 August 2024).

3. DEFINITIONS

See Annex 1 Glossary.

4. ANNEX 1 INTERPRETATION – QUESTIONS & ANSWERS

4.1 Section 1 – Scope

Scope (Q#1)	Is the CCS (Contamination Control Strategy) also applicable for manufacturing of non-sterile products?	Yes, it can be applicable. When a company does not manufacture sterile medicinal products, but for example has grade C/D cleanrooms and use of these cleanroom classes is deemed necessary to assure the quality of non-sterile products, e.g. low bioburden product, the CCS still has its importance. In general, the manufacturer should evaluate the possible risks of contamination based on its process and product knowledge and consideration of the manufacturing conditions, facilities/equipment and raw materials used for the processes and define appropriate risk-mitigating measures as required. It is up to the respective company to define how it maps these assessments and the resulting strategies (e.g. within a summarising CCS document). If Annex 1 requirements are followed, a document should be available that describes which principles have been applied and how compliance with those principles is demonstrated. See also Annex 1 Scope, where it is stated that “Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.”
Scope (Q#2)	What are the expectations for sites that, due to the design of, for example, their facilities or equipment, don't comply with the new requirements defined in the new Annex 1 without significant remodelling/reconstruction of said facilities or equipment?	All requirements should be fulfilled by all manufacturers. If these could not be met immediately at the time of publication of the new Annex 1, a risk-based assessment of a non-compliant situation should be performed and interim actions to mitigate the risks defined, including appropriate timeframe to bring the facility into a compliant situation.

4.2 Section 2 – Principle

2.1iv	Does 2.1(iv) imply that all raw materials and packaging materials should have bioburden and endotoxin/pyrogen	Each material should have an adequate specification, addressing its intended use and potential risks to quality of finished products, and where applicable in compliance with relevant monographs and/or dossier.
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	specifications and that they should be tested whenever the manufacturer receives them?	Each delivery should be adequately tested. CCS justifies testing approach, e.g. based on the nature of the material, lifecycle supplier qualification activities, its intended use and the testing history/trends. Typically, material used in topical ophthalmic or inhalation products are not requiring endotoxin/pyrogen specifications. See also answer for 10.2.
2.3 (Q#1)	How frequently should the effectiveness of the CCS be reviewed?	Continued suitability of the CCS should be assured on an ongoing basis. As results are obtained, they should be actively reviewed for consistency with the established strategy to confirm that CCS performance remains aligned with expectations. Furthermore, it is recommended that the effectiveness of CCS should be reviewed at a minimum during the management review, the CCS should be also reviewed regularly as part of the ongoing quality management, during significant change or deviation, in the event of a significant emerging problem, and during the periodic product quality review. Accordingly, the minimum review frequency should be annual.
2.3 (Q#2)	Does the CCS need to be one document? What should be the structure of the CCS?	There is no set requirement for the format of the CCS. The content to be included has been clarified, and given the need for periodic updates and review, it is essential to use a structured document allowing proper management and implementation. The format and detailed structure are secondary factors; what is important is that each element that makes up the CCS is properly identified, described and evaluated and that a system is established for regularly reviewing the CCS. The importance of the elements included in the CCS varies depending on the product manufacturing process, facilities and equipment used. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood. The CCS should ensure that the implemented control strategies deliver effective and consistent control across the entire manufacturing facility and drive continual improvement.

4.3. Section 3 – Pharmaceutical Quality System

No questions.

4.4 Section 4 – Premises

4.12 (Q#1)	Paragraph 4.12, point ii, states that only materials and equipment that are on an approved list and that have been assessed during validation of the transfer process, should be transferred into grade A or grade B areas via airlocks or pass-through hatches. What does “validation of the transfer process” mean?	The validation should demonstrate that the process is achieved without introducing contamination. In addition, the methods used to sterilise/disinfect the materials should be validated. Effective transfer, sterilisation processes, properly sealed packaging, rapid transfer systems for isolators or bacterial retention filters need to be verified.
4.12 (Q#2)	Is it always required to strictly adhere to the area cleanliness cascade (i.e., respecting the sequential order of cleanroom classes) for material transfer through airlocks or pass-through hatches or is it possible to skip a grade (e.g., moving materials from unclassified area directly to class C) under certain circumstances?	For material transfers into higher grade cleanrooms, it is not strictly required to always adhere to the area cleanliness cascade. Under certain circumstances, it is possible to skip a grade <i>for transfers of materials into grade C</i> , when fully compliant with the Annex 1 requirements.
4.19	What would be the expected airflow regime in grade A when handling powders?	The airflow for powders should adhere to the principles of Annex 1. Paragraph 4.30 in Annex 1 refers to a homogeneous air speed range of 0.36 - 0.54 m/s (guidance value). Should the manufacturer determine that air speeds within this range present a potential contamination risk related to the velocity of the air, then a different airspeed would be allowed when scientifically justified in the CCS. Please see also Q&A 4.30.
4.20	What is meant in paragraph 4.20 by the need to take into consideration, among others, the “extent of automation” when carrying out CCS related risk assessments of an isolator?	This means that (current) automated functionalities and processes associated with the use of the isolator (e.g. the bio-decontamination process) and the activities taking place inside (e.g. the manufacturing process) should be included in the CCS related risk assessment. For new isolators, such risk assessments should be carried out as part of the design, qualification or selection of the isolator system. The risk assessment should be revised or supplemented during the lifecycle of the equipment and

		processes, as knowledge and experience increases or in the event of changes being implemented.
4.21	Is VHP an acceptable sterilisation method for gloves?	Annex 1 does not list vaporized hydrogen peroxide (VHP) as a sterilant due to its lacking robustness and ability to penetrate materials. Instead, VHP is referenced solely in the context of surface bio-decontamination, which is not equivalent to sterilisation. Where sterilisation is required, a validated sterilisation method specified in Annex 1 (paragraphs 8.50 to 8.78) should be used, unless the company can demonstrate that the robustness and penetration ability of VHP provides an equivalent level of sterility assurance, especially with regard to the cleanliness and flawlessness of the surface to be treated and in relation to the specific material or surface that is to be rendered sterile. Where bio-decontamination is permitted by Annex 1 (e.g. RABS gloves), a validated VHP process may be used.
4.22 (Q#1)	Are manual operations accepted for bio-decontamination?	The bio-decontamination process for an isolator should be an automated process. However, paragraph 4.22 refers to both RABS and isolators, and manual bio-decontamination processes are commonly encountered for RABS. Such manual processes should be designed in such a way as to be reproducible and to cover the entire surface area of the equipment, and their robustness and effectiveness should be demonstrated by appropriate validation and by regular monitoring.
4.22 (Q#2)	“Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator”. How should this be demonstrated?	The cleaning or bio-decontamination procedure should include steps designed to effectively remove cleaning agent or disinfectant (including sporicidal agent) residues from the RABS/isolator. The effectiveness of these steps should be demonstrated based on validation data (refer to Annex 15, cleaning validation). For isolators, validation data should be available to demonstrate that the residual amount of sporicidal agent at the end of the sporicidal cycle is below the concentration that could be detrimental to the product quality and stability. Control mechanisms should be defined to ensure that the conditions prevailing during validation support effectiveness of the conditions used during routine operation such that when measured at the end of the cycle, the residual

		concentration of sporicidal agent will be below the maximum permitted level. The extent to which samples are to be taken during validation and analysed for disinfectant/cleaning agent residues can be defined based on a risk assessment, taking into account the risk of transferring such residues to the product or a product contacting surface. The assessment of potential adverse impact should also be extended to the potential for ingress of bio-decontamination agent ingress into containers, goods or materials present during gassing. For example, aseptic compounding requiring the gassing of products, syringes and bags before processing.
4.22 (Q#3)	Beside the use of VHP as a decontamination agent, can VHP be considered a sterilant?	Annex 1 does not list vaporized hydrogen peroxide (VHP) as a sterilant due to its lacking robustness and ability to penetrate materials. Instead, VHP is referenced solely in the context of surface bio-decontamination, which is not equivalent to sterilisation. Where sterilisation is required, a validated sterilisation method specified in Annex 1 (paragraphs 8.50 to 8.78) should be used, unless the company can demonstrate that the proposed VHP process provides an equivalent level of sterility assurance, taking into account the limited penetration capability and recognised fragility of VHP, particularly with respect to surface cleanliness, surface defects, occluded areas, environmental conditions and the specific materials and surfaces to be sterilised.
4.22 (Q#4)	Are other disinfectants acceptable, other than H ₂ O ₂ ?	Yes, Annex 1 leaves room for novel disinfectants and sporicides with appropriate validation of their effectiveness.
4.27	Are maximum limits for ≥5.0 µm particle size count required during cleanroom qualification/requalification?	Maximum limits for ≥5.0 µm particles are not a default requirement during classification of grade A (at rest and in operation) and grade B (at rest). However, monitoring of particles ≥5.0 µm for compliance with defined limits is required during routine operation and as stated in Annex 1, classification (qualification/requalification) including 5µm particles may be considered where indicated by the CCS or based on historical trends. When there are no maximum limits, this decision should be supported by documentation and the CCS. Therefore, the CCS should include consideration of whether classification limits for >5.0µm particles are appropriate.

4.29i	What equipment should be operational/installed during cleanroom classification?	It is the expectation that all equipment that will be used in the manufacturing area has been installed before cleanroom classification, as these could impact airflow patterns and particle measurements. Any such equipment should be present for the 'in operation' classification. If the equipment is intended to be "on" at all times, it should also be "on" during classification. If equipment will be switched off when activities are not occurring in the room, it should be off during at rest qualification.
4.30	Is it acceptable for barrier technology systems with unidirectional air flow to have air speed at the work position outside the range of 0.36 – 0.54 m/s (guidance value) provided in Annex 1?	Yes, where this is scientifically justified in the CCS and meets the requirements for unidirectional air flow, as described in Annex 1. Furthermore, airflow visualization studies should correlate with the air speed measurement and demonstrate protection of the critical process operations (first air protection).
4.32	Are viable and total particles measurement both required during requalification of a cleanroom?	Cleanroom classification (total particle concentration measurement at rest and in operation) is required for clean room requalification. Measurement of viables is not explicitly required for requalification, however, the requirements as listed in section 4.32 are the minimum requirements that should be included. Any other requirement should be included when found necessary from e.g. trend analysis and/or risk assessment (see also section 9.4, 9.9, 9.13).
4.33	Is a disinfectant rotation program necessary?	A disinfectant rotation program is not a requirement. However, it is required that more than one type of disinfecting agent is used, including the periodic usage of a sporicidal agent. The use of disinfectants and sporicidal agents in a rotation, where the agents are alternated on a defined schedule, may be an effective approach to the cleanroom disinfection program. Independent of the use of a rotation program, the disinfection program should be shown, in formal validation, to be effective against anticipated levels of surface contaminants, bacteria, and fungi. Furthermore, it is important that the effectiveness of the disinfectant program should be monitored as part of the ongoing quality management, during a significant change or deviation, in the event of a significant emerging problem, and during the periodic product quality review.

4.5 Section 5 – Equipment

5.5	Is it possible to consider a vapour-phase hydrogen peroxide (VHP) cycle as the sterilisation method for the stopper bowl and other indirect contact parts?	Annex 1 does not list vaporized hydrogen peroxide (VHP) as a sterilant due to its lacking robustness and ability to penetrate materials. Instead, VHP is referenced solely in the context of surface bio-decontamination, which is not equivalent to sterilisation. Where sterilisation is required, a validated sterilisation method specified in Annex 1 (paragraphs 8.50 to 8.78) should be used, unless the company can demonstrate that the proposed VHP process provides an equivalent level of sterility assurance, taking into account the limited penetration capability and recognised fragility of VHP, particularly with respect to surface cleanliness, surface defects, occluded areas, environmental conditions, and the specific materials and surfaces to be sterilised. Where manual assembly of indirect product contact parts of equipment is required after sterilisation, bio-decontamination with VHP after assembly can be a useful risk-reduction tool as part of the overall contamination control strategy, alongside the other requirements for aseptic assembly outlined in Annex 1.
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4.6 Section 6 – Utilities

6.10	In relation to the measures to minimise risk of microbial growth during the distribution of Water for Injection (WFI), are other alternatives than constant circulation of WFI at a temperature above 70°C acceptable?	Although constant circulation at a temperature above 70°C is highly recommended and well-established practice, recirculating systems operating at lower temperatures (including ambient or cold loops) may be necessary. In such situations, there have to be much stricter sterilisation and/or sanitation methods and monitoring measures in place, which are properly justified and validated to effectively minimise or prevent microbial growth and avoid other contamination. These measures include, but are not limited to, more frequent sanitisations, extensive sampling programs or tighter in-house alert limits for bioburden testing. Further guidance on controls for microbial risks of water systems is described in point 6.12 of Annex 1. Additionally, compliance with design, construction and maintenance requirements indicated in the “Water systems” section of Annex 1 should be ensured.
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6.13 (Q#1)	What is the sampling frequency for regular ongoing chemical and microbial monitoring of WFI?	A suitable sampling schedule for water for pharmaceutical use should be in place to ensure that representative water samples are obtained for analysis on a regular basis. Sampling plans should be designed to detect development of any adverse trends in the quality of the water and be commensurate with the risk; consequently, for WFI distribution systems, sampling plans should be much more stringent. Quality control sampling locations in the main WFI distribution system should include all points of use (POUs) and all outlets, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis, defined based on qualification data and QRM principles. As indicated in Annex 1, at least one representative sample tested for chemical and microbial should be taken every working day of the water that is used for manufacturing processes (i.e. from a manufacturing POU); the selection of this POU should be based on a risk assessment. It should also be considered to sample the worst-case location defined using QRM every working day in order to provide additional assurance of the quality of water utilised in the manufacturing processes.
6.13 (Q#2)	Is online monitoring at the return loop sufficient or is offline monitoring additionally needed?	Online monitoring alone is not sufficient, as it typically includes only TOC and conductivity measurements. As noted in point 6.13, comprehensive chemical and microbial monitoring of water systems is required to ensure continued compliance with compendial expectations, which includes also the return loop. Therefore, the return loop sampling point should be included in the offline monitoring plan to assess additional parameters beyond TOC and conductivity, such as microbiological contamination and bacterial endotoxins.
6.17	Does point 6.17 apply to the steam used in autoclaves for the sterilisation of equipment or materials?	Yes, point 6.17 applies to all steam used as a direct sterilising agent, including, but not limited to, Sterilisation in Place (SIP) and autoclave cycles used for sterilising equipment and materials.
6.19	Point 6.19 indicates that, when gases are used in the process, microbial monitoring of the gas should be performed	Annex 1 emphasises that microbial monitoring (viable particles) of process gases at the point of use needs to be performed at a higher frequency based on risk. Other parameters (e.g. oil or water content) should be tested at a sufficient

	periodically at the point of use. Does this mean that during routine production, it is only necessary to perform microbial monitoring of process gases and it is acceptable to monitor other parameters (e.g. oil or water content) during qualification and requalification?	frequency to ensure the appropriate chemical and particulate quality of the gas (see point 6.18 of the Annex 1). This monitoring frequency, defined in the CCS, should be in line with the qualification and requalification requirements established in Annex 15 and Annex 1.
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4.7 Section 7 – Personnel

7.4	The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. What are the critical steps in the initial qualification of operators to perform activities in the grade A and B areas? How should these steps be co-ordinated before access is allowed?	Personnel shall successfully complete an initial and ongoing qualification programme covering gowning, aseptic behaviour and techniques prior to access to Grade A and B areas. The programme should include a documented visual assessment of gowning against defined acceptance criteria and a post gowning microbiological assessment at critical locations (e.g. gloves, forearms, chest and hood/facemask, as applicable). For initial qualification, microbiological assessment should be repeated in sufficient number of runs to demonstrate the consistency, and performed at least once for requalification. Results should comply with established limits (ref. Annex 1, §9.30), with appropriately defined alert and action levels per plate and overall. After a full investigation of the root cause of failure(s), qualification should be repeated until acceptance criteria are met, with a risk-based limit on the number of attempts. Only personnel who have successfully completed gowning qualification may participate in an Aseptic Process Simulation (APS). Successful APS participation is required before granting unsupervised access to areas where aseptic operations are in progress (including all activities which could compromise aseptic operations). For manual operations, APS design and execution should consider the requirements of Annex 1, §9.39 and include qualification of the specific interventions the operator is authorised to perform.
7.6	Point 7.6 states that there should be systems in place for the disqualification of personnel from working in	Personnel may be disqualified from unsupervised cleanroom access due to inadequate hygiene, adverse personnel monitoring trends, involvement in a failed APS, non-compliance with

	or given unsupervised entry into cleanrooms that is based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring programme and/or after being implicated in a failed APS. What are some further examples of disqualification events? How would disqualification be implemented and what would be the conditions of requalification?	aseptic or cleanroom practices, failure to maintain qualification or prolonged absence from cleanroom activities/cleanroom gowning, noncompliance with EU GMP Chapter 2 requirements, etc. Disqualification should be managed through a documented procedure defining triggers and actions, including restriction of cleanroom access. It may involve informing the relevant personnel, revoking access badges and updating access control systems, as applicable. Requalification should be risk-based and may include retraining, repeat gowning qualification and, where applicable, successful APS participation. Access should be reinstated only when appropriate, and after documented completion of requalification activities.
7.14	Point 7.14 states that outdoor clothing including socks (other than personal underwear) should not be brought into changing rooms leading directly to grade B and C areas. Does this apply for terminally sterilised manufacturing activities?	Yes. Point 7.14 applies to the manufacture of all sterile products, including those that are terminally sterilised. The requirement aims to prevent the introduction of contaminants into changing rooms leading directly to Grade B and C areas.

4.8 Section 8 – Production and specific technologies

8.10	In the case of aseptic processing, would it be acceptable for the dispensing room to be grade D rather than grade C, provided that the materials are dispensed under laminar flow located in this room?	No, according to Annex 1, sampling and dispensing for aseptic processing, should be performed in, at least, a grade C environment. This is a minimum requirement for processes that include a sterile filtration step. Grade A with appropriate background as described in point 4.20 is required if there is no further sterile filtration in the process.
8.17	Are all interventions (e.g. all inherent interventions regardless of their type and duration) required to be recorded in batch documents during processing?	Yes, all interventions during the aseptic processing should be documented in batch records. The extent of detail of documentation is linked to the potential impact on grade A and/or product quality. This includes both inherent and corrective interventions. A description of the intervention activity, the time and duration of the activity, and the operator(s) involved is required. Interventions should be recorded in order to ensure that they are performed in a manner as

		validated during APS, and, for any given intervention, at no greater frequency than that established during the APS. The records should provide full batch traceability including reconciliation of the number of removed units in order to allow the authorised/qualified person to determine whether the sterile product has been manufactured in accordance with the approved process and to facilitate investigation of environmental monitoring excursions and contamination events.
8.23 (Q#1)	What is the expectation for routine integrity testing of flexible IV bags (a final products) with a volume <100mL) that are filled and then closed by a non-fusion method, (e.g. stoppered)?	As the body of the bag is typically formed by fusion (welding), irrespective of the method used to finally close the bag, (e.g. gluing of a port or stoppering and crimping) these units should be subjected to 100% integrity testing, in accordance with paragraph 8.22.
8.23 (Q#2)	Products using closure systems other than fusion should be taken and checked for integrity using validated methods. Does it mean that every batch to be tested?	CCIT should be carried out on a representative sample of these products using a validated method that is appropriate to demonstrate integrity for the given type of closure. Assuring proper integrity of closure system is a critical element of sterility assurance, thus CCIT is typically considered for each batch, when the knowledge is gained through the testing operations. Depending on the CCS and the product closure design, the frequency of CCIT can be reduced, but that would not be acceptable for example in case of modification of the closure system supply chain or in case of vials closed under vacuum.
8.36, 8.38, 8.39	What should be considered when determining which loading patterns should be used for initial and periodic autoclave (re) validations?	Initially, each sterilisation process and loading pattern should be validated. Manufacturers should utilise QRM principles in determining the frequency for revalidation of each sterilisation loading pattern, considering the complexity of the sterilisation process, the level of cycle control and monitoring, and the overall risk of cycle failure to product quality. Where a suitably representative “worst-case” load is identified (e.g., same material, loading pattern, cycle, etc), and scientifically justified based on validation and monitoring data, it may be acceptable to perform at least annual re-validation of the “worst-case” load, with all other sterilisation loads subjected to periodic revalidation at a frequency justified in the CCS.

8.50	What are the general expectations regarding the use of redundant probes/independent monitoring systems for heat sterilisation cycles?	Redundant probes serve as a backup to the primary process monitoring probes, ensuring continuous cycle monitoring in the event of probe failure or inaccuracy. Redundant probes should be connected into a monitoring system that operates independently from the control circuit for the steriliser, in order to detect any discrepancies or failures in real-time. These probes should be strategically placed to monitor critical parameters like temperature and pressure throughout the sterilisation cycle. This requirement aims to ensure that any sensor failure or drift is detected, preventing the release of improperly sterilised goods. Results of all probes should be reviewed during batch certification and release.
8.63	Moist heat sterilisation: Is it expected that routine re-validation includes a temperature mapping for systems where steam in place is used for sterilisation?	Yes, routine (or periodic) validation should include tests providing evidence that the positions used for routine temperature monitoring throughout the sterilisation process still represent the slowest to heat locations (aka cold point) during sterilisation.
8.67	How to interpret the requirements related to the sterilization/disinfection of a depyrogenation tunnel?	Evaluation of the depyrogenation tunnel, especially the cooling zone, should be included in the CCS and disinfection/sterilisation frequency justified by QRM. Examples of factors to consider may include, validation data, tunnel design especially the belt design, activities that may have environmental impacts such as after maintenance, shut down, or other activities that may lead to the interruption of the first air supply, environmental monitoring data/trends, etc.
8.87, 8.92	In the case where redundant filtration is used, is it necessary to perform a pre-use post sterilisation integrity test (PUPSIT) for both the primary and the secondary (redundant) filter?	PUPSIT testing should be performed for those filters which are declared as being potentially used to support the batch release. If the redundant filter is not subject of PUPSIT, it can't be used to demonstrate a successful product sterilizing filtration step if primary filter fails post-use testing.
8.87 (Q#1)	Is it mandatory to perform PUPSIT of all sterilising grade filters used in manufacturing?	Paragraph 8.87 requires PUPSIT to be performed for filters used for the final product sterilisation, (e.g. solutions or liquids), whenever feasible. While PUPSIT is not mandatory for other sterilising filters used in production processes, (e.g. upstream control of bioburden), the integrity testing of these filters should be performed based

		on risk, and in accordance with the CCS, (refer paragraph 6.19)
8.87 (Q#2)	What are the circumstances where PUPSIT may not be possible?	Verification of the integrity of sterilising filters before and after use is a requirement. PUPSIT provides assurance of product sterility and therefore patient safety. Manufacturers should consider process design changes or modifications in order to implement PUPSIT; however, in the event that PUPSIT is not feasible due to process constraints that are not linked to design flaws, an alternative approach may be acceptable, provided it is justified within the CCS, supported by a comprehensive product and patient safety focused risk evaluation and appropriate risk mitigation measures are adopted. However, risk assessments should not be used inappropriately to justify the omission of PUPSIT.
8.112	Are routine revalidation studies using viable bacterial spores expected for the validation of extrusion systems?	The validation of extrusion systems should include studies that demonstrate appropriate sterilisation capability. While initial validation studies should include the use of bacterial spores and demonstration of inactivation, their use for requalification should be based on a product and patient centred risk evaluation. Manufacturers should determine critical process parameters for extrusion, e.g. temperatures, extrusion speeds, polymer mass, etc. and utilise physical measurement and recording data to demonstrate ongoing control of validated processes.
8.118	Which areas are unwetted during sterilisation as defined in paragraph 8.118ii?	When the manufacturing process requires the addition of a separately fabricated component to a BFS container, and this connection forms the critical product fluid path, manufacturers need to ensure that the surfaces between the component and moulded container are appropriately sterilised. Sterilisation of these surfaces may be readily achieved where the heated product in the container can directly access the connection surfaces during moist-heat sterilisation. However, where the surfaces are not directly exposed to the product in the container, and there is no moisture in the area between the component and moulded container, there is a risk that heat transfer is achieved only through conduction, and thus sterilisation of these areas may not be achieved.

		Manufacturers should consider the risk of the creation of areas that are not directly wetted during sterilisation and take precautions to ensure these "dry pockets" of critical fluid pathways are effectively sterilised in the manufacturing and assembly process.
8.122	Is VHP a suitable method for lyophiliser sterilisation?	Annex 1 does not list vaporized hydrogen peroxide (VHP) as a sterilant due to its lacking robustness and ability to penetrate materials. Instead, VHP is referenced solely in the context of surface bio-decontamination, particularly for applications such as material transfer airlocks and isolator systems. Where possible, moist heat sterilisation is the method of choice. Other methods should only be considered if moist heat sterilisation is not applicable due to the limitations of the process or materials. In the case of lyophilisers, it is well-known that it is possible to design and operate steam sterilisable equipment. Where lyophilisers are just bio-decontaminated by VHP and not sterilised, this should be considered as a deficiency.
8.123	What is the exact expectation of 8.123 with respect to the reduction of operator interventions, as opposed to using manual loading? Are companies expected to implement this at some point in time, e.g. when a new lyophiliser is introduced? Or will manual loading always be allowed?	Human intervention should be minimised as much as possible by appropriate technological and organisational measures to prevent contamination by eliminating or mitigating hazards. Wherever possible, contamination risks should be minimized by replacing manual activities with automated solutions. When the requirement to sterilise manually loaded lyophilisers with no barrier technology separation before each cycle is fulfilled, manual loading/unloading using appropriate rigorous contamination prevention safeguards is still currently allowed. However, since the CCS should drive continuous improvement, the manufacturer should take appropriate decisions based on the risks identified and should seek alternatives in order to mitigate the risks.
8.128, 8.130	Can the sterility of the critical, product-contact surfaces of a closed system be assured if the system is opened in a cabinet with Grade A laminar airflow (LAF)?	According to Annex 1, a closed system is defined as a system in which the product is not exposed to the surrounding environment and is not opened until the process is fully completed. Once the system is opened it will no longer be considered as closed. As specified in paragraph 8.130, if a closed system is opened, for example, during maintenance of a bulk manufacturing line, this intervention should be conducted in a classified

		area appropriate to the material and the type of process. For processes involving terminal sterilisation, at least a Grade C environment is required. For aseptic processing, the intervention should occur in a Grade A environment, either within a Grade B background or inside an isolator installed in a Grade C or D area, depending on the isolator's design. Alternatively, if such interventions are not performed in a suitably classified area, the sterility barrier is breached, and the potential contamination risk of the product should be assessed. Before reusing, the system should undergo appropriate cleaning and disinfection, and for aseptic processes, sterilisation is also required before resuming operations.
8.128 (Q#1)	Are non-aseptic connections allowed to be carried out for coupling closed systems if a sterilisation cycle (SIP) occurs prior to use?	Yes, such approach is possible, provided that the SIP process subsequently used is appropriately validated and the material of the connectors (e.g. plastic) is resistant against the SIP conditions and the integrity of the sterile core is maintained. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility.
8.128 (Q#2)	Is the use of intrinsic sterile connectors purchased from qualified suppliers permitted as a suitable strategy to connect sterile equipment to each other and may the end-user rely on the sterility documentation (sterilisation validation) provided by the respective supplier?	Provided that the supplier of the aseptic connector in question was covered by comprehensive qualification activities and the validation package/data provided by the supplier for the connector (e.g., validation of the gamma irradiation process, data on microbial challenge tests, etc.) have been checked and found to be sufficient, and that the supplier is subjected to periodic re-evaluation, the end-user can rely on such data, but should cover this equipment and its handling during the Aseptic Process Simulation (APS). See also paragraph 8.139 on single-use systems. If single-use connectors that are sterilised by the end-user (e.g., by autoclaving) are used for coupling sterile systems, this sterilisation process should be validated. It should also be ensured that single-use connectors are suitable for sterilisation and that the latter does not impact their functionality or integrity (e.g., by causing the material of construction to become more porous).
8.128 (Q#3)	Is tubing welding considered suitable for aseptically connecting equipment parts	According to the Annex 1 glossary, intrinsic sterile connection device can be mechanical or fusion sealing. As long as the equipment is qualified, the fusion process is validated (e.g., by microbial ingress test), the connections are

	maintaining the closed status of a system?	covered in the APS and the system can be shown to remain integral at every usage, tubing welding can be used as an intrinsic sterile connection suitable for closed systems.
8.129, 8.137, 8.138	For single-use systems, can system integrity tests performed by the respective suppliers be leveraged without the end-user having to carry out their own tests?	Whenever possible, the integrity of critical single-use systems should be tested by the end-user on site (i.e., before and/or after use in production, depending on the risk of compromising the sterility of the product). It is acknowledged that such an integrity test, e.g., by means of a pressure hold test using an inert gas, is difficult to establish for some single-use systems and is also only reliable to a limited extent. However, the decision in this respect should be justified by well-founded measures and considerations, be verified by risk assessments and should be included in the CCS. The possibility of relying on integrity test results provided by the respective suppliers for single-use materials (such as bags) requires a detailed assessment of the situation, taking into account, among other things, the severity of impact of possible integrity deficiencies on the manufacturing processes/product quality and their detection probability during the process. The adoption of integrity results from the vendor requires an in-depth qualification of the supplier, including possible on-site audit to ensure the reliability of the tests performed by the vendor, and should also take into account the risks of subsequent damage to the single-use material during its delivery and installation in production. The user should also ensure that the complete assembly is covered by the integrity test performed by the supplier and not only specific components.
8.133, 8.134, 8.135, 8.136	To what extent can end-users of Single-Use Systems (SUS) rely on supplier-generated data—such as validation packages, extractables studies, and compatibility assessments—and when are additional end-user studies, including leachables testing, necessary?	End-users are encouraged to consider relevant supplier-generated data in the evaluation of SUS in support of their suitability for use. Reliance on supplier-generated data, its review and justification for acceptance should be documented with the PQS. As stated in 8.135, the interactions of the product and the SUS should be evaluated under process conditions. The end-user is responsible for the detailed review of the supplier-generated documentation, ensuring that its contents meet the end-user's standards and requirements and that the conditions used by the suppliers when generating the data are representative of actual

		(or worst-case) production conditions. Quality risk management should be utilised in determining the requirement for and extent of additional studies, verification or validation activities performed by the end-user. Detailed consideration should be given as to how representative the supplier-generated data is to the end-user's processes, the criticality of the SUS used in the intended process, the robustness of established control strategies at the end-user which allow detection of possible SUS defects (e.g., pressure hold test, extensive program of microbiological testing during the process), etc. End-users of SUS are expected to risk-assess and evaluate the results of extractable/leachable studies, to determine whether the intended product or process is at risk from extractables/leachables, taking into account the route of administration of the respective drug (e.g., oral, parenteral, subcutaneous), the dosing frequency to a patient, the use of the respective SUS in the process (e.g., use in early or late manufacturing step), the composition of the product and the contact time of the process solution/product with SUS surface. The outcome of the evaluation, necessary safety assessments and any need for additional extractable/leachable studies should be documented. Based on an assessment of such aspects, it may be possible for the end-user to scientifically justify that no leachable studies are performed for products, where no patient risk is identified. As extractable/leachable studies are required as part of the filing dossier for Marketing Authorization, end-users should align their strategy with the requirements of the Marketing Authorization or, if necessary, with the respective regulatory authority.
8.134	What are the expectations placed on the assessment of Single-Use Systems (SUS) suppliers and what should it comprise? Would an on-site audit of the supplier/manufacture of an SUS be expected?	The supplier assessment/qualification should cover the supplier delivering the SUS but, in particular, the SUS manufacturer (or each relevant manufacturing site, if the SUS in question is produced at several sites) and any sub-contractors involved in critical services or processes (e.g., sterilisation of the SUS). The supplier assessment/qualification should be carried out in parallel with the evaluation of the SUS material and should play a crucial role in the SUS selection decision.

		Based on QRM principles and as defined by the CCS, a Quality Agreement should be in place with the supplier. This Quality Agreement should cover the SUS specifications as well as quality-relevant and product lifecycle conditions. The end-user of SUS should apply QRM principles in determining the extent of supplier qualification activities for manufacturers of SUS. End-users are normally expected to perform an on-site evaluation of the manufacturer/supplier of critical SUS (or have evidence of the site compliance) to ensure that effective controls for assuring critical quality attributes of the SUS are in place. It is expected that audits cover all systems, relevant processes and control strategies (e.g., sterilisation process and its validation, subcontractor qualification, in-process culling of defects, defect rates etc.) considered critical for the respective SUS and these contents should be comprehensively documented in the respective audit report.
8.134, 8.138	What should the incoming goods inspection at the end-user include to comply with paragraph 8.134 & 8.138?	Checks detailed in 8.134 and 8.138 should be carried out and documented prior to use and not exclusively during the incoming goods inspection. Each assessment should be conducted by personnel appropriately trained for that assessment and in conditions that avoid contamination of the product. Due to the special nature of SUS and their delivery in packaging that serves to protect them from damage but does not allow for a full visual inspection of the materials, the scope of a feasible routine incoming inspection program upon receipt is generally very limited. Immediately upon receipt, in accordance with paragraph 8.138, an initial documented inspection of the shipment should be performed, consisting primarily of a review of the documents provided by the supplier, a visual check of the integrity of the outer packaging, label printing, and a reasonably cursory verification of the contents of the shipment (without complete unpacking of the SUS to avoid the risk of damages). Later examination should consist of at least a deep visual inspection of the SUS by qualified employees according to an established procedure, the results of which should be documented as part of the batch record. The visual inspection should include verification of the compliance of the SUS with approved technical

		drawings, the presence of gamma irradiation indicator labels (if applicable), and a visual examination for integrity of the system (e.g., inspection of the welds, connectors, absence of critical scratches, etc.) as well as for the absence of particulates. If technically practicable and indicated in the CCS, the integrity of the single-use system should be verified by means of a pressure hold test.
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4.9 Section 9 – Environmental and process monitoring

9.9	When do we expect more stringent action limits than defined in Table 5 and 6?	Annex 1 mentions that the need for more stringent action limits could result from data trending, the specific nature of the respective processes and considerations within the CCS. Depending on the results of the environmental monitoring (when for example there have been no excursions over a long time period) and the associated trend assessments, the capability of the plant should be reflected in the more stringent Alert and/or Action limits to ensure that emerging adverse trends are identified in a timely manner.
9.10	What statistics do we expect for establishing alert levels?	Annex 1 does not establish which method is to be used for establishing alert levels. The manufacturer should define the method and document it in the quality system. For a new process where limited data for environmental monitoring is available, it is acceptable to establish an alert limit based on the results of cleanroom qualification tests. When more data becomes available the alert level limits should be evaluated from the environmental monitoring data to ensure that the alert setting takes into account recent historical behaviour, trends. Alert level limits should be reviewed regularly by the company and be adapted, if necessary, based on the actual performance of the underlying contamination controls.
9.17	Can the measurement of total particles be performed with a lower flow rate?	It is not generally acceptable to use lower flow rate for monitoring of total particles. Text of Annex 1 point 9.17 is clear and describes minimum rate of 28 litres per minute for total particles.
9.22, 9.30	Is justification required for not performing all the environmental monitoring methods indicated in 9.30,	Annex 1 captures the minimum requirements expected. When it is not possible to perform some of the controls because of intrinsic limitations of the process, a formal risk

	Table 6, for routine monitoring for a specific grade?	assessment should identify alternative controls that are necessary to put in place to ensure that the same level of assurance is provided.
9.22, 9.23, 9.28, 9.29, 9.31	Is it possible to fully replace microbiological monitoring using e.g. settle plates and volumetric air sampling systems, by other integrated sampling and testing systems (e.g. Rapid Microbiological Methods, RMM)?	Paragraph 9.22 requires microbial monitoring using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling. New technologies are available such as continuous active air sampling and rapid microbial testing system, e.g., based on digital imaging technology to detect and count growing microbes. Equivalence or superiority of rapid methods should be demonstrated, and the suitability of the chosen method should be proven, including for local isolates. Validation data of these new methods should include recovery studies of the sampling method. The exposure time should not have any negative effect on the suitability of the media used. The colonies should be isolated and identification of microorganisms should be performed in grade A and B, and performed in C and D when action limit is exceeded, as it is essential to determine the (possible) root cause of a contamination and evaluate the risk of contamination for the drug product. Consideration should be given to identifying organisms also in case of alert limit excursions. Some rapid methods do not allow for the identification of the underlying contaminant. Such systems may be used only as rapid alert systems, in support of traditional monitoring methods, where there is a requirement to perform identification as described above.
9.30	Do the limits indicated in 9.30, Table 6, apply to passive airborne viable monitoring using settle plates exposed for less than 4 hours? Or are tighter limits necessary for recoveries on settle plates exposed for less than 4 hours?	The limits in table 6, 9.30, are per plate and no tighter limits are necessary for a shorter exposure time (less than 4 hours). The exposure time should not be deliberately shortened to avoid positive results. Additionally, the sum of all viable particles found in same one position by using multiple plates should be within specification expected for exposure for max. 4 hours. Settle plates should be exposed in grade A and B areas for the duration of operations including aseptic equipment set-up and in grade C and D areas as determined based on QRM.
9.33, 9.36 viii	What should be the duration of the APS used to simulate a very long	During the APS, it should be demonstrated that the maximum filling duration does not pose any risk.

	filling process (e.g. 96 hours filling process)?	The whole filling time needs to be covered during the initial validation of the APS in order to establish the maximum filling time, including evaluation of extended line stops. For the subsequent APS, a risk-based approach needs to be applied, with the whole filling time covered at defined intervals. All shifts need to be covered at least for the full shift length, and other aspects should also be taken into consideration, e.g. holding times, incorporation of worst-case manipulations and interventions, shift change-over activities (8.18).
9.34 (Q#1)	What does “frequency” mean here? Absolute number of interventions or how often do they occur during a certain time interval?	Frequency in this context means the absolute number of interventions that occur during the routine aseptic process. These should be included in the APS. Any reduction of the number of each standard interventions during APS (e.g. in case of high number of vials in the filling process), should be justified by QRM and not be used to overcome a poorly designed or poorly controlled process. Additionally, non-standard interventions should be covered.
9.34 (Q#2)	What interventions should be included in the APS for the annual operator’s requalification?	As part of the annual requalification each operator should perform each type of intervention that they are expected to perform during routine activities. These interventions should be representative for the aseptic intervention on the respective line and process during the manufacturing and are discussed in Annex 1 paragraphs 8.16, 8.17 and 8.113. They should be in line with the authorised list of allowed and qualified interventions.
9.36ii (Q#1)	What does “same container/closure configuration” mean?	This refers to the dimensions (e.g. diameter of opening), the shape and material of the container and closure. For example, a stopper for lyophilization has a different shape than a stopper for liquid products; this is considered a different container/closure system.
9.36ii (Q#2)	There is a filling line followed by lyophilisation. Can the liquid filling with subsequent lyophilization be considered as worst case, such that APS performed under these conditions would also cover liquid filling process without lyophilization?	Liquid filling and lyophilisation are usually different processes on the same line, with different paths and different container closure systems. Therefore, the initial APS for liquid and lyophilisation should be carried out separately, so that initial APS (3 batches) needs to be conducted for both processes. For follow up APS, if there is a high degree on similarity of the 2 different processes/ presentations, a common APS for both

		processes needs to be justified by QRM. A high degree of similarity of the 2 different processes is essential. However, both paths should be reflected in the APS program with an appropriate frequency.
9.36ii (Q#3)	Is a bracketing approach possible for the APS with more than one lyophiliser?	No. If there are multiple lyophilisers for one filling line, no bracketing approach can be applied. Each lyophiliser and its transfer path needs to be covered by APS. In case of multiple lyophilisers combined with multiple filling lines, the APS program has to cover all lyophilisers and all filling lines. If supported by QRM based on a sound scientific rational, a bracketing approach may be possible, considering risks related to different transfer paths between different filling lines and different lyophilisers. However, it has to be ensured that all lyophilisers, their worst-case transfer paths and all filling lines are covered by the APS programme with a minimal frequency every half yearly as defined by Annex 1. Inclusion of different transfer paths into APS program should be based on QRM principles, assuring that all used transfer paths are included in sufficient frequency. If not, individual APS is necessary for each combination.
9.36ii (Q#4)	When can a bracketing or matrix approach be applied?	If equivalence of different combinations can be shown (e.g. glassware and stoppers), a bracketing approach can be applied for the APS. New materials should be qualified, and an APS is part of the qualification. The bracketing approach is further described in the glossary of Annex 15 (Qualification and Validation).
9.36iii (Q#1)	Should maximum hold times for sterile bulk be included in the APS for aseptic filling?	Any holding time after final sterilisation of the bulk should be included in the APS.
9.36iii (Q#2)	How should the maximum permitted holding times for sterile equipment exposed during the aseptic process be covered in the APS? Is it the maximum permitted holding time since the sterilisation or after assembling/opening the packaging?	The various holding times to be minimised and limited to a defined and validated maximum time for aseptic processing as defined in Annex 1 8.18. When developing the APS plan consideration should be given to holding times for sterile product and sterile equipment that is exposed during the aseptic process. The quality system should define the holding times and how they are calculated. The APS plan should identify which holding times will be simulated in the APS and ensure that the APS imitates the routine process as closely as possible.

		9.36iii refers only to the maximum holding times of sterile equipment during exposure. The exposure of sterile equipment starts with assembly and includes the whole filling process, as 9.36iii states "exposed during the aseptic process".
9.36v	When should anaerobic APS be performed?	In case the aseptic process is conducted under anaerobic conditions, or an anaerobic monitoring identifies contamination, an anaerobic APS should be carried out periodically. This should be assessed and documented in the CCS.
9.36xii and xiii	Does the APS of campaign manufacturing require the simulation of the maximal number of batches and duration of a campaign?	A campaign is defined by Annex 1 as "<i>A manufacture of a series of batches of the same product in sequence in a given period of time with strict adherence to established and validated control measures.</i>" The procedure and scope for the initial and the subsequent routine APS program should be defined based on a sound risk assessment so that the APS approach supports the maximum time and number of batches of the campaign. The initial validation of the campaign duration needs to be covered in three APS runs (whole duration, maximum number of batches, all critical parameters and interventions, etc.). The subsequent routine APS format will vary depending on how the campaign and batch changeover is performed. It may be appropriate for an APS at the beginning and APS at the end of a campaign, with real product production in the middle section of the campaign. The approach to APS should not put product batches at increased risk, for example filling product after media without a full cleaning/ decontamination/ sterilisation process. However, end of campaign APS should not replace routine APS. The number of vials to be filled during the single APS runs might be reduced considering the requirements of paragraph 9.40.
9.38 (Q#1)	For a validated isolator system, is it acceptable to perform APS once a year as ISO 13408-1(2023) 8.2.5.1 specifies for highly aseptic process in highly validated isolator system?	No, ISO 13408-1 does not override Annex 1 requirements. Annex 1 states 'normally APS should be repeated at least twice per year' for each aseptic process, each filling line and each shift. This frequency reflects general expectations and is in line with best practice for sterility assurance.
9.38 (Q#2)	How many APS runs should be performed for	For infrequently used lines/processing areas, the same APS requirements along with other controls required by Annex 1 apply as for

	infrequently used lines or processing areas?	frequently used lines: initially with three consecutive runs, then normally twice a year (every 6 months). An APS should also be considered before a long period of inactivity to provide data to support previously manufactured batches (e.g. last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line). If a line is not used for a longer period of time, and the routine APS programme has not been maintained, a new initial APS with three batches would be expected.
9.45	Can the inspection of filled APS units be performed by production personnel (trained and qualified)? Do they need to be independent of the APS process (i.e. they should not have participated in the APS run that produced the units they are inspecting)?	If the production personnel are properly trained, qualified and able to distinguish contaminated containers from non-contaminated ones, the inspection of filled APS units can be performed by production personnel. In this case it needs to be ensured that the responsibilities between those whose process is being validated and those validating the process is clearly segregated, e.g. by performing APS inspection by independent production personnel of the APS process under supervision of QA/QC.
9.45ii	Should Growth Promotion Test (GPT) of APS media be performed directly on the vials or could it be conducted with a pool of samples? What is the inoculum size?	GPT is performed wherever possible by inoculating the actual APS containers with the organisms to include all the potentially inhibiting factors related to container/closure system or to the process. In addition to reference organisms required by Pharmacopoeia, GPT should also include local isolates and be performed with an inoculum size in accordance with relevant Pharmacopoeia (e.g. of ≤ 100 CFU). To better mimic the process, an inoculum in the lower range is preferable.
9.46 (Q#1)	After a failed APS, with identification of root cause and corrective actions implemented, would it be acceptable to resume production prior to the 14-day reads off test and completion of successful growth promotion (with batches at risk if a repeat failure occurs)? Release of batches could only resume after completion of successful revalidation (3x APS)?	Annex 1 clearly states <i>production</i> should resume only after completion of successful revalidation (9.46 vii). Due to higher risks linked to the failed APS, the production and certification of at-risk batches is possible only if APS was successful and all deviations were investigated and closed.

9.46 (Q#2)	After a failed APS run, when can a reduction of 3 consecutive repeat APS be justified?	Normally, a minimum of 3 consecutive repeat APS should be conducted after a contaminated unit (failed run). Any alternative approaches should have data to support that an equivalent or superior level of assurance is achieved.
9.49	APS after long shutdown: What is an extended period of time for 9.49i?	If the specific aseptic process has not been in operation for an extended period of time, but the APS programme and other controls (e.g. facility qualification, cleaning, maintenance, environmental monitoring) have been maintained, then it is likely that the routine APS programme can be relied upon to support the aseptic process resuming. However, if the APS cannot be performed two times a year, for each shift and filling line, it is an "extended period of time" by definition. In this case, the initial validation of the aseptic process should be repeated prior to resuming the aseptic process.

4.10 Section 10 – Quality control (QC)

10.2, 10.3	Should bioburden be tested on each batch of raw material as incoming control AND on the product before its sterilisation?	The need for microbiological testing of raw materials/ packaging materials in accordance with their adequate specification is covered by Q&A to paragraph 2.1iv. In case of products as stated in Annex 1, the bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products immediately before the final sterilising grade filter or the terminal sterilisation process. Annex 1 also states that where overkill sterilisation parameters are set for terminally sterilised products, bioburden should be monitored at suitable scheduled intervals. In addition, provisions for bioburden monitoring for products authorised for parametric release are provided in point 10.4 of Annex 1.
10.3	Is it acceptable to set bioburden monitoring frequency on risk-based approach following ISO 13408-2?	No. ISO 13408-2 does not override Annex 1 requirements.
10.6	Is there any requirement for room classification of a QC Microbiological laboratory when isolators are used for testing?	When a closed isolator is used, and meets aseptic conditions, the area in QC laboratory surrounding the isolator needs to assure there is no negative impact on the testing and its results. It should be reflected in the CCS and supported

		by a risk assessment with scientific/technical based rationale, that selected configuration is maintained in a state of control and provides an appropriate level of contamination control consistent with Annex 1 requirements.
10.6iii	What does “different lyophilisation loads” actually mean when sampling for sterility testing?	Different lyophilisation loads means each lyophilization cycle from each lyophiliser used.

10. REVISION HISTORY

Date	Version Number	Reasons for revision
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