Interpretation of GMP Annex 1 2022 (Rev. 1)

Document valid from:	**31.10.2023**	
Document number:	**I-SMI.TI.25e**	**Version 1.0**
Classification:	**Public**	
Replaced document:	**--**	dated: --
Root SMI documents:	**--**	
Referenced QMI documents:	**--**	

Approval	Date:	Signature:
Author:	23.10.2023	Barbara Herzog
Technical verification:	27.10.2023	Federico Cimini
Formal verification (Release VS-QMI):	31.10.2023	Michelle Scheidegger

Index

1 Purpose and scope

This technical interpretation focuses on some of the most important main changes of the revision 2022 of Annex 1 and also covers aspects that were already included in the previous version of this guideline and that repeatedly gave rise to questions. This technical interpretation is intended to reflect the general opinion of the Swiss Inspectorates on these topics and to serve as a support during the inspection of manufacturers of sterile medicinal products.

2 Basics

The Revised Annex 1 to the PIC/S GMP Guide (PE 009), about manufacture of sterile medicinal products, 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 will become binding from 25 August 2024).

3 Definitions and abbreviations

n.a.

4 Interpretation: Questions and Answers

4.1 Scope (Annex 1, Chapter 1)

Q&A No.	Paragraph No.	Questions	Answers
1	Chapter 1 (Scope)	Does Annex 1 apply without restriction also to ATMPs or are only defined aspects of Annex 1 to be followed for some specific product types, such as for example the allogeneic and autologous cell therapy products?	It is recognised that ATMPs cover a very heterogeneous range of products and that for some of these products, due to their nature and manufacturing technology, specific considerations are required. This certainly applies, for example, to the allogeneic and autologous cell therapy pro-ducts, which are to be manufactured under conditions suitable to avoid microbial contaminations, but which usually cannot be terminally sterilised or sterile filtered. In addition, such products are made from unsterile patient material. Specifically with regard to cellular therapy, Annex 2A, paragraph 5.29(b), requires that aseptic processing be maintained from the time of procurement of cells through manufacturing and administration back into the patient. Annex 2A refers to Annex 1 several times (e.g., in connection with the requirements for the provision of systems for closed processing), but implies the possibility of exceptions from applying the requirements of Annex 1. It must also be taken into account that Annex 2A became valid in May 2021, i.e., more than one year before the publication of the new Annex 1 version.

			It is expected that ATMP manufacturers, based on the knowledge of their manufacturing processes and the execution of detailed risk analyses covering all process steps, materials and systems, develop and implement Contamination Control Strategies suitable to avoid or largely minimise risks of product contaminations. Justification must be given for any exceptions to the requirements of Annex 1.

4.2 Premises (Annex 1, Chapter 4)

Q&A No.	Paragraph No.	Questions	Answers
2	4.1, 4.11 & 4.12	Are grade A and B cleanrooms required to have separate airlocks for material and personnel and must the flows in such airlocks be strictly unidirectional?	In general, it is expected that new facilities have for grade A and B zones segregated airlocks for personnel and material and that the flows in such airlocks are unidirectional (i.e., separate MALs for transport into and out of the cleanroom and separate PALs for personnel entry and exit). Existing facilities that do not have such airlock separation must ensure that, as a minimum, temporary separation of the flows in the airlocks is guaranteed and that the situation is covered by scientifically sound risk analysis also assessing the need of additional technical or organizational measures. The rationale for not applying physical separation of the above-mentioned flows through segregated airlocks and the risk assessment on which it is based must be integrated in the overall contamination control strategy.
3	4.12	Paragraph 4.12, point ii, states that only materials and equipment that are on an approved list and that have been assessed during validations 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, for example for the material transfer into an isolator?	As mentioned in paragraph 4.10 of Annex 1, the transfer of materials, equipment or components into and out of a cleanroom (incl. the critical zone within a grade A environment), represents one of the greatest potential sources and risks of contamination. In order to minimise such risks, great care must be taken in particular when defining the technical and procedural measures associated with the transfer of materials/equipment into an aseptic processing area. Only in relatively rare cases it is possible to bring materials into an isolator before it is sealed and bio-decontaminate them together with the isolator using a validated VHP treatment

			(only possible for small batches and if materials are resistant to VHP). In the majority of cases, however, it is necessary to transfer materials to an isolator that has already been decontaminated. For this, all materials must first be sterilised and then moved through the physical barrier of the isolator in such a way that the sterility of the goods and the integrity of the isolator are maintained. Regardless of the technology used (e.g., usage of double-door sterilisers upstream of the isolator, use of transfer isolators or of rapid transfer port technology), the entire transfer process must be considered within detailed risk analysis and be part of the overall contamination control strategy. In addition, appropriate control mechanisms must be defined to monitor the maintenance of the integrity and functionality of the systems (e.g., measurement of differential pressure and control of door interlocks between adjacent zones of the transfer system). The technical solutions must be covered by appropriate equipment/system qualifications (incl. smoke studies if applicable) and sterilisation validations and the suitability of the entire transfer process must be verified through APS (validations and also regular APS). Appropriate qualification measures and APS must also be used to demonstrate that the egress of materials from the isolator does not affect the maintenance of the grade A zone requirements. The arrangement of the installations, the processes carried out in it and the material movements must also be considered when defining the points to be sampled during PQ activities or during routine or event based environmental monitoring.
4	4.12	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 from CNC directly	Compliance with the cleanroom sequence for the transfer of materials via airlocks or pass-through hatches is expected to be fulfilled for zones A and B (exceptions from this rule are possible for sterility test rooms). For cleanroom areas with lower classification, it is principally feasible for materials to be transferred from one low zone (CNC) through an airlock or pass-through hatch

		to class C) under certain circumstances?	directly into an area with two grades higher classification (grade C area), provided that suitable technical and/or procedural measures are established ensuring fulfilment of the cleanroom specifications in the respective areas. The adequacy of the established systems/procedures needs to be demonstrated by appropriate qualification activities and the results of regular environmental monitoring. The defined measures and the risk analyses on which they are based must be part of the CCS.
5	4.20	What are the expectations for older barrier technology systems that do not meet all the requirements according to the new Annex 1? By when do they have to be replaced or upgraded?	The company has to perform an in-depth internal evaluation of the current barrier technology and assess whether the installation, its cleanroom background and all related systems/procedures meet the requirements of the new Annex 1 or whether technical measures are required. If necessary, a project has to be initiated for example to upgrade the cleanroom used as background and install additional airlocks. From August 25th 2023, all barrier technology equipment not complying with the revised Annex 1 are considered deficient and deviations will be issued upon findings during inspections. Depending on the CAPA plan and interim risk reducing measures defined, an additional implementation timeline of approx. one year may be acceptable.
6	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 refers to the inclusion in such CCS risk assessments of an evaluation of all automated functionalities and processes associated with the use of the isolator and the activities taking place in it (from cleaning and disinfection of the equipment, to the transport of materials into the isolator, their handling and the product filling, to the capping and removal of the filled containers). The use of a well-designed, automated, recipe-controlled and possibly robotised system, equipped with appropriate control and alarm systems, can increase the reproducibility of the operations and minimise both errors and manual interventions. Ideally, such risk analyses should already be carried out as part of the design or selection of the isolator system and should be revised or supplemented during the lifecycle of the

			equipment, as knowledge and experience increases or in the event of changes to be implemented.
7	4.22	Are manual operations accepted for bio-decontamination?	The decontamination process for an isolator should always be an automatic process. However, paragraph 4.22 refers to both RABS and isolators, and manual decontamination processes are most commonly encountered for RABS. Such manual processes must be designed in such a way to be reproducible and to cover the entire surface area of the equipment, and their robustness and effectiveness must be demonstrated by appropriate validation and by regular monitoring.
8	4.22	"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 direct and indirect product contact surfaces within the RABS/isolator. The effectiveness of these steps should be demonstrated based on validation data. For isolators, validation data should be available to demonstrate that the residual amount of sporicidal agent is below the concentration that could be detrimental to the product quality and stability at the end of the sporicidal cycle. Control mechanisms must be defined to ensure that the conditions prevailing during validation are also maintained during routine production (e.g., compliance with the time after completion of the sporicidal cycle, resp. measurement of the peroxide concentration). The extent to which samples of the surfaces 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 of a packaging component.
9	4.30	Is it acceptable that for barrier technology systems with unidirectional air flow other air speed and speed measurement positions are defined than those mentioned in Annex 1?	The most important requirement for barrier technology systems stated in paragraph 4.30 is that the air velocity in unidirectional airflow systems must be defined in such a way that unidirectional and uniform airflow conditions prevail at the working positions where high-risk operations

			take place, suitable to protect the product and open components (e.g., containers) from contamination. The air speed range of 0.36 - 0.54 m/s is, as stated in the above paragraph itself, merely a guideline value that has been encountered in the pharmaceutical industry for decades. Annex 1, however, clearly allows for the establishment of alternative air speed ranges or measurements at different heights in the system than the working position, provided this is “scientifically justified in the CCS”. It is important that the suitability of the defined airflow conditions is proven by airflow visualisation studies (part of the system qualification) covering the entire system and that these are correlated with the respective defined air speed range at specified height/position. The air speed must be measured continuously during operations and kept within this defined range.

4.3 Utilities (Annex 1, Chapter 6)

Q&A No.	Paragraph No.	Questions	Answers
10	6.12	Water generation - reverse osmosis system: What are the requirements regarding the sanitization (disinfection) of the system?	Paragraph 6.12 gives detailed guidance on the requirements. It is important that the system is designed to allow for routine sanitization / disinfection and a procedure is in place defining this regular preventive sanitization or disinfection of the RO-system. It should also include a regular change of membranes. The frequency of sanitization should be determined based on quality risk management principles and on the data gathered during the qualification of the system, and it should be reviewed at least annually taking into consideration the routine monitoring data. The system must continuously be maintained meaning that the sanitization also has be performed when no production is running or when no water is used for production.
11	6.13	What are the sampling requirements for regular ongoing monitoring of Water for Injection?	A suitable sampling schedule should be in place to ensure that representative water samples are obtained for analysis on a regular basis. For

			WFI distribution system sampling plans are more important because microbial control must be much more stringent. In general, water sampling for microbial and bacterial endotoxin testing is expected to occur daily somewhere in the system, with each outlet being sampled periodically to characterize the quality of the water. The use of cold loops requires a much closer microbiological monitoring and special sanitization measures. Quality control sampling locations in the main distribution system should include all POUs, having also process control sampling be located before the first and after the last POU and at other specified worst-case locations. POU sampling plans should rotate through all use points on the system, with the expectation that samples are collected on a daily basis from various use points, and that all use points are sampled on a rotational basis. The loop return should be sampled each day of use of the system in order to provide additional assurance of the quality of water utilized in the manufacturing processes. For WFI, it is an expectation that water samples should be taken daily from a minimum of one POU, with all point of use tested weekly during the qualification phase. The final phase of qualification may form the basis for the ongoing sampling frequencies with the goal of ensuring that the system is maintained in a validated state. However, it has become good industry practice to continue to utilize the same sampling frequency beyond the completion of the performance qualification to collect sufficient historical data in order to justify adjusting the sampling frequency. The use of risk analysis tools coupled with stringent periodic data review may be used to alter the frequency of sampling. Any decrease of the sampling frequency for routine monitoring should be based on historical data and should only occur when a large number of historical data is available to allow statistical analysis. Based on the outcome of analysis of data and on the regular review of the performance of the point of use or the system, and if

			operational SOPs are in place which ensure also an increase of the sampling frequency if indicated and regular maintenance activities, e.g. for all outlets, a less frequent sampling can be justified. The risk assessment should consider the fact that decreased sampling frequencies also results in a higher number of batches that will be put at risk and a problem may have a serious impact on supply of products for patients.
12	6.19	Where should process gas be monitored?	The monitoring of process gas should be performed as close as possible before the sterilization filter (the level of contamination before sterilization should be under control to ensure the efficiency of the gas sterilization process).

4.4 Personnel/Training (Annex 1, Chapter 7)

Q&A No.	Paragraph No.	Questions	Answers
13	7.4	This paragraph requires that all personnel accessing grade A and B areas be trained in aseptic gowning and aseptic behaviors. It also stipulates that compliance with the gowning procedure must be confirmed by means of assessments and periodic reassessments on an annual basis, covering both visual and microbiological checks (monitoring of gloved fingers, forearms, etc.). Are these assessments to be covered by staff participation in APS? Paragraphs 9.38 and 9.39 mention staff participation in APS only in the context of staff requalification. Do APSs also have to take place during the initial qualification of employees? Does every employee have to perform every manual intervention in APS in order to be qualified or requalified?	To ensure product quality, adequate training of employees working in grade B and A areas or involved in aseptic processes (incl. the necessary preparatory activities) is essential. The qualification must be adapted to the respective activities of the single employee and, after initial training (initial qualification), must also include regular requalification / retraining. Annex 1 requires that each employee qualified and involved in aseptic processes participates in a successful APS at least annually (or every six months if the aseptic processes are manual) as part of his requalification. However, Annex 1 is not specific about the scope of the initial employee qualification, but indicates in paragraph 7.4 that the relevant training must cover theory and knowledge transmission as well as practical aspects and that evidence of training effectiveness is required through assessments using both visual and personnel monitoring examinations. Although not explicitly required in Annex 1, the expectation for the initial qualification of an employee for the aseptic area is that practical process simulations, including manual interventions, are carried out under the supervision of

			qualified trainers/QA and are followed by personnel monitoring as training verification. It is at the discretion of the respective pharmaceutical company to define and justify whether these process simulations need to be conducted separately (but under similar conditions as an APS) or can be integrated within an APS. It is important that the representativeness of the activities to be performed by the trainee for the actual processes is justified and that the simulations cover each critical activity to be carried out by the respective employee. Equivalent representative interventions can be grouped for staff qualification. All operators should perform one intervention per year from each group of equivalent representative interventions.

4.5 Production and Specific Technologies (Annex 1, Chapter 8)

Q&A No.	Paragraph No.	Questions	Answers
14	8.36 & 8.38 / 8.39	Sterilisation: what are the required loading patterns for initial and periodic autoclave (re-) validations?	Initially each loading pattern must be validated. Re-validation of each loading pattern must be done annually. If a suitable worst-case load (the same material, same loading pattern, same cycle) for re-validation (backed up with data) can be identified, not every load of this material needs to be re-validated. A theoretical reference load is not acceptable, as 8.36 states that “each type of load” needs to be validated.
15	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 sterilization?	Yes, routine (or periodic) validation should include tests providing evidence that the positions used for temperature monitoring throughout the sterilization process are still representative of and correspond to the slowest to heat locations during sterilisation.
16	8.128	Is the sterility of the product-contacting surface of a closed system ensured if the system is opened in a cabinet with laminar airflow (LAF)?	Opening a sterile, closed system should be avoided whenever possible. In general, a closed system that needs to be opened should be returned to the sterile state by carrying out a validated sterilization process (if required, preceded by cleaning).

			If a sterilisation of the system after opening is not possible, the system's opening could be performed in a decontaminated isolator (provided that the introduction of the closed system to be opened or relevant parts of it into the isolator does not compromise the isolator's decontamination status and can be considered covered by successful APS). Opening the system in an LAF with classification A and background B could possibly be an alternative to the isolator but rather to be envisaged in exceptional cases only as the risks of introducing contamination from the environment are higher and require appropriate consideration and risk mitigating measures.
17	8.128	Are non-aseptic connections allowed to be carried out for coupling closed systems if a sterilization cycle (SIP) occurs prior to use?	Yes, such an approach is possible, provided that the SIP process used is appropriately validated.
18	8.128	Is the use of sterile aseptic connectors purchased from qualified suppliers permitted as 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 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 sound, the end-user can rely on such data, but must cover this equipment and its handling during his manufacturing process APS activities. See also paragraph 4.6.4 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 must be validated. It must 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).

19	8.128	Is it considered acceptable to introduce small amounts of product or cells into a sterile closed system with a syringe fitted with a needle through a septum? Can the system be considered closed after piercing of the septum?	Such a practice should be avoided for aseptic steps, as piercing a septum with a needle is to be regarded as a breach of the sterile barrier. In aseptic processes where the above approach is used, measures must be taken to re-design and optimise the procedure accordingly. If the process concerned cannot be improved and adapted immediately, consideration should be given, as a temporary measure, to minimise the risk of contamination, as to whether the syringe should be left with the needle inserted in the septum after completion of the material addition and appropriately secured in this position. In addition, it should be considered that the top of the septum (prior to piercing) be protected by a sterile film, which is removed just prior to insertion of the syringe needle to reduce the risk of contaminants on the septum surface entering the process and avoiding treating the septum with a disinfectant, which may also pose a risk of contamination of the product (by disinfectant residues).
20	8.128	Is tubing welding considered a suitable strategy for aseptically connecting equipment parts maintaining the closed status of a system?	Welding equipment and processes must be qualified/validated. If such processes are used in sterile or aseptic filling processes, they must be covered also by APS. However, as tubing welding processes are both less monitorable and entail risks of undetected integrity deficiencies, such practices should be avoided and more reliable systems should be used, which should be taken into account whenever possible already during facility and process design.

21	8.129	Closed systems: in case of using single-use systems, can system integrity tests performed by the respective suppliers be leveraged without having to carry out own tests?	Whenever possible, the integrity of critical single-use systems should be tested by the end-user on site (i.e., before use in production). 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 small single-use bags/containers and is also only reliable to a limited extent. However, the decision in this respect must be justified by well-founded measures and considerations, be verified by risk assessments and must be included in the CCS. The possibility of relying for single-use materials (such as bags) on integrity test results provided by the respective suppliers requires a detailed assessment of the situation, taking into account, among other things, the criticality 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 and must also take into account the risks of subsequent damage to the single-use material during its delivery and installation in production.
22	8.134	Single-use systems: what are the expectations placed on the assessment of such suppliers and what must it comprise?	The supplier assessment should be understood as a comprehensive qualification of the single-use systems (SUS) supplier. This assessment/qualification should cover not only 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) as well as 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. For all SUS that the end-user intends to use in his manufacturing process and that will have direct contact with the product, intermediates, process solutions or starting materials/raw materials, a Quality Agreement should be concluded with the respective supplier. This Quality Agreement should cover the SUS specifications as

			well as quality relevant service conditions (e.g., requirement to manufacture SUS in cleanrooms) and regulate, among other things, the terms relevant for the notification of planned changes and their approval by customers, the procedures in the event of major/critical deviations impacting delivered SUS, the terms in case of customer complaints and the oversight responsibility for sub-contractors. Supplier qualifications must include an assessment of the supplier's quality systems, a comprehensive review of all relevant technical documentation received (incl. for example drawings, documentation of components used such as filters, aseptic connectors, tubings etc., certificates and validation/study packages), and audits. It is expected that audits cover all systems, relevant processes and control strategies (e.g., sterilisation process and its validation, subcontractor qualification, etc.) considered critical for the respective SUS and these contents must be comprehensibly documented in the respective audit report.
23	8.138	What aspects should be taken into account by the end-user when determining the acceptance criteria of the respective SUS and in which form should they be specified?	Acceptance criteria should be defined taking into account the intended use of the particular SUS in the manufacturing process, the criticality of its use/impacted process, existing process knowledge, as well as available SUS experience. Acceptance criteria should encompass quality aspects (e.g., sterility, biocompatibility, visible particles testing by compendial method, integrity tests, certificates, etc.), functionality (e.g., inserts and components required, temperature resistance in operating range, autoclaving or freezing resistance, chemical compatibility, substainable pressure, packaging requirements, etc.) as well as validation/qualification requirements to be fulfilled by the SUS and its supplier. According to Annex 1, paragraph 8.132, the use of SUS and the associated risks should be also assessed as part of the Contamination Control Strategy, taking into account the fragile nature and potential complexity of the SUS in question, possible interactions of the SUS surfaces with

			the product, risks associated with manual operations/connections and risks of holes or particle contaminations. The resulting conclusions from these assessments and any risk mitigating measures should be taken into account, if appropriate, when establishing the SUS acceptance criteria and the expectations placed on the SUS suppliers. To comply with the requirements of paragraph 8.138, according to which the conformity of the SUS with the approved specification has to be checked upon good receipt, the quality requirements should be defined in a written specification (including or referencing a technical drawing of the material). The other expectations regarding the functionality of the SUS or the expected validation / qualification/study package to be made available by the supplier and to be agreed with the supplier, can be defined in another document, such as a SUS user requirement document, an annex to the Quality Agreement, or similar.
24	8.138 & 8.134	What should the incoming goods inspection at the end-user include to comply with paragraph 8.138 & 8.134?	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). On the basis of a positive result of this first incoming check, the SUS can be released, allowing its transfer to the production area to be subjected to a more thorough examination. This examination must consist at least of a deep visual inspection of the SUS by qualified employees according to an established procedure, and the results of which must 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 points (if applicable and as evidence of the sterilization), and a visual examination for integrity (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, the integrity of the single-use system should be verified by means of a pressure hold test.
25	8.134	Is it considered acceptable that some study or validation data provided by SUS suppliers (e.g., validation packages incl. sterilization or material chemical and biological compatibility data) are incorporated by the end-user into his own assessments without the need to carry full studies/validations on his own?	When looking at the wording in the paragraphs on single-use systems (SUS), it can be concluded that Annex 1 allows principally the adoption by the end-user of data received from qualified suppliers. However, this requires that the end-user confirms through a detailed review of the respective documentation that its contents meet the user's standards and that the conditions used by the suppliers when generating the data are representative (or worst-cases) for its own actual production conditions. The extent of the end-user's own studies/verifications or validations activities depends on the representativeness of the supplier data, the criticality of the intended SUS use in the process, established control strategies at the end-user which allow detection of possible SUS deficiencies (e.g., pressure hold test, extensive program of microbiological testing during the process), etc. For example, an end-user operating in the biotech area must verify with own studies or assessments whether possible leachables emitted from the films of a single-use bioreactor can negatively affect the growth of cells and it is also the responsibility of the end-user to verify or provide data to prove whether absorption effects of its product on the SUS surface are possible, resulting in an impact on product quality (see paragraph 8.132, «…*These risks include but are not limited to*: *i. the interaction between the product and product contact surface (such as adsorption, or leachables and extractables)*»). When SUS are used in the sterile production, it is mandatory that they are covered by APS, as required in paragraph 8.139. For cell culture (or

			fermentative) processes, the end-user should evaluate the need to perform a process simulation before starting routine production to confirm the suitability, integrity, and handling of the SUS equipment.
26		Do end-users have to carry out their own extractable studies or can they use the supplier's data and when is it necessary to execute leachable studies?	Most SUS suppliers provide comprehensive extractable studies packages to end-users. In recent years, efforts have been undertaken by international industry working groups to harmonize and standardize the conditions for extractions and analysis of extractables. Additionally, many suppliers also provide certificates covering the product contact films, e.g., Biological Reactivity Test in Vivo per USP <88>, Class VI. It is expected that based on the package of extractables data obtained, the end-users evaluate the adequacy of the data provided, potentially "add together" data from different SUS components, and define the need for additional extractables studies to simulate process-specific worst-case conditions and perform health safety assessments, as appropriate. The decision to carry out leachable studies with the respective product is usually based on a comprehensive evaluation of the possible risks of administering leachables in doses that may be of concern when using the respective drug product. In addition to the results of the extractable data and any resulting safety assessments, the decision regarding the need for a leachable study should take 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) and the contact time of the process solution/product with SUS surface. Based on an assessment of such aspects, the company may justify that no leachable studies are performed for products that are still in the clinical phase and/or are only administered infrequently (e.g., vaccines). Since extractable/leachable studies are part of the filing dossier for marketing authorization, it is necessary to align the strategy with the requirements of the marketing

			authorization or, if necessary, with the respective regulatory authority.
27	8.80	Is it expected that there are two redundant sterilizing filtration steps in the process before aseptic filling?	Annex 1 encourages an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible. The installation of such a redundant sterile filter significantly reduces the risk of a product quality impact in the event of a failed filter integrity test, which is why this risk-minimising measure is to be considered state of the art process and should be used especially for new processes. The risks and impacts of filter integrity failures of pre-fill point sterile filters should be assessed as part of the CCS evaluations and the decision not to install a redundant sterilising filter be justified in the CCS. Even in the case of using two sterilising filters, any filter integrity failure that may have occurred should be investigated.
28	8.83 / 8.84	Paragraph 8.83 makes reference to the relevant Pharmacopeia requirements in relation to the validation of sterile filtration of fluids. Which paragraph of the Pharmacopeia should be considered for this purpose?	Relevant guidance can be found in Ph. Eur. 5.1.1, paragraph “Membrane filtration/Filtration effectiveness” and in guideline EMA/CHMP/CVMP/QWP/850374/2015. Useful details and expected data/methods can also be found in PDA TR26 “Sterilizing filtration of liquids”.
29	8.91 / 8.92 / 8.93	Is a pre-use / post-sterilisation integrity testing (“PUPSIT”) of sterilising grade filters used in aseptically processes mandatory?	The expectation is that PUPSIT be applied to verify the integrity of the sterilized filter assembly. However, paragraph 8.87 allows some flexibility in justified cases supported by risk analysis and covered in the CCS.

4.6 Environmental & Process monitoring (Annex 1, Chapter 9)

Q&A No.	Paragraph No.	Questions	Answers
30	9.4	What is deemed regularly (“These risk assessments should be reviewed regularly”)? How often does the risk assessment need to be reviewed?	It is not possible to give definitive guidance here, because, as ICH Q9 (R1) states, the frequency of Risk Review should be based on the level of risk. The frequency or timing of a Risk Review exercise may be based on the type and number of risks identified during an earlier Risk Assessment exercise, and on the extent of risk control that was required to mitigate risks. It

			may also depend on the level of uncertainty (i.e. lack of knowledge) that was present during an earlier risk assessment. The higher the level of uncertainty in relation to risk estimates and the related risk-based decisions, the greater the need to review those estimates and decisions at an early timepoint once such uncertainties have been reduced. An environmental monitoring trend report will be compiled every year and depending on the results, the risk assessment might be reviewed. It should be assessed annually if the review of the risk assessment is required. Swissmedic recommends to review the risk assessment regularly, e.g. for a new plant it is recommended to reassess the RA after one year when more experience and knowledge have been gained.
31	9.9	When do we expect more stringent action limits?	More stringent action limits might be necessary if the trend data shows very low levels of detection of total particles and viable particles with no action limit excursions over a longer time period (e.g. one year).
32	9.10	What statistics do we expect for establishing alert levels?	For a new process where limited data and experience for environmental monitoring data is available, it is acceptable e.g., to calculate the alert level limit based as 50% of the action level limit. When more data becomes available the alert level limits should be statistically from the environmental monitoring data to ensure that the alert setting takes into account its own recent historical behaviour. Traditionally the “2 or 3 standard deviation rule” (alert level = Average value + 2 x SD) which assumes the data is normally distributed, has been applied. As environmental monitoring data are usually not normally distributed, other statistical approaches such as a nonparametric approach based on 99.9Th or 99.99th percentiles, a nonparametric tolerance limit approach, or a cut-off Value approach (e.g., at 59th or 99th percentiles) should be used. Alert level limits should be reviewed regularly by the company and be adapted, if necessary, based on the actual performance. Performance

			based alert levels that are well below the action limits should be considered as a confirmation of solid microbial control of the environment.
33	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 a microbial monitoring using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling. New technologies are available as continuous active air sampling and rapid microbial testing system, e.g., based on digital imaging technology to detect and count growing microbes. Equivalence of methods should be demonstrated and the effectiveness of the chosen method should be proven, including for in-house germs. 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. For the use of real-time viable particle counting and given the non-equivalency AFUs versus CFUs and current GMP / Pharmacopeial limits are in CFU, the company need to collect data on their process for the real-time viable particle counting to compare it to the standard environmental monitoring data. A full understanding of what triggers signals and what is a normal AFU signal in the process and the development of appropriate alert and action limits based on this data, together with appropriate procedures that should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring must be established. A scientific justification for the limits applied is required. Data must be available for at least 12 months. Required elements the company needs to have: – Primary Validation Package of the vendor for the system – User specific Validation Package / Data for Verification of Validation ▪ Parallel phase grade A (RRM/traditional active air sampling method) in operation to gain experience with new technology under grade A

			▪ Test for interferences to be addressed, e.g., by disinfectants, materials or product – Operational Approach: Implementation / Alarm Handling Concept – Supportive data: Collection and evaluation of data in a production area grade C and D Identification of microorganisms must be performed as it is essential to determine the (possible) root cause of a contamination and evaluate the risk of the contamination for the drug product. If an action limit exceedance occurs, the agar plate from the system must be incubated in order to isolate associated CFUs and to allow identification of species for further investigation and impact assessment of product quality.
34	9.34	What means “frequency” here? Absolute number of interventions or how often they occur during a certain time interval?	Frequency means that the absolute number of interventions that occur during the routine aseptic process should be included in the APS.
35	9.34	What interventions should be included in the APS for the annual operator’s requalification?	Each operator should perform each intervention. The worst case must be covered, which means that the interventions are independent of the lot size and the duration of the production. See in more detail in the Chapter above about Personnel (Annex 1, paragraph 7.4).
36	9.36ii	What does “same container/closure configuration” mean?	“Same container/closure configuration” refers to the dimensions, (e.g. diameter of opening) shape and material of the container and closure, like e.g. vial/stopper. E.g. has a stopper for lyophilisation a different form than a stopper for liquid products, this is therefore considered a different container/closure system.
37	9.36ii	There is a filling line with subsequent lyophilisation. Can the liquid filling with subsequent lyophilization be considered as worst case, so that APS of liquid filling with lyophilization would cover as well liquid filling process without lyophilization?	No, liquid filling and lyophilisation are different processes on the same line, with different paths.
38	9.36ii	When can a bracketing or matrix approach be applied?	If equivalence can be shown between e.g. glassware and stoppers a bracketing approach can be applied for the APS. New materials must

			be validated and an APS is part of the validation.
39	9.36xii & xiii	Does the APS of campaign manufacturing require the simulation of the maximal number of batches and duration of a campaign?	This is a complex question and the scenario depends on many factors. Consideration should be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating the campaign duration does not pose any risk. The start-of-campaign (including aseptic assemblies if the case) AND end-of-campaign studies should be conducted in any case.
40	9.46	Can we differentiate between 1 CFU and >1 CFU like in ISO 13408-1 (2015) for 5'000 10'000 and > 10'000 units filled: if 1 CFU is detected, investigation, and consideration of one APS, if > 1 CFU, investigation, corrective measures and repetition of validation with 3 APS runs?	No. The new Annex 1 is stricter than the ISO 13408-1 (2015). Any contaminated unit with a contamination > 0 CFU results in a failed APS and actions according to chapter 9.46 should be followed.
41	9.46	With identification of root cause and corrective actions implemented, would it be acceptable to resume production (with batches at risk if a positive) prior to the 14-day reads off test and completion of successful growth promotion? Release of batches could only resume after completion of successful revalidation (3x APS)?	No, as it clearly states, that PRODUCTION should resume only after completion of successful revalidation (9.46 vii)

4.7 Quality Control (QC) (Annex 1, Chapter 10)

Q&A No.	Paragraph No.	Questions	Answers
42	10.1	To support the design of manufacturing activities, environmental monitoring regime etc., Annex 1 requires that personnel with appropriate training and experience in microbiology and sterility assurance should	Microbiological knowledge (incl. sterility assurance) can be acquired by education, training and experience. The best prerequisite for the involvement of a person as an expert, for example in CCS assessments, the definition of resulting measures or in investigations on microbial contaminations,

		be available. What is considered appropriate training and experience?	is an education (in particular a university degree or an equivalent diploma e.g. an institution of higher technical education) in the field of microbiology (or possibly other natural sciences, or medicine). However, a good understanding of the manufacturing processes concerned is also required.
43	10.2	What limits do we expect for specifications for raw materials, components and products? What is typical?	The need for microbiological testing of raw materials and the limits to be defined for such testing should take into account the nature of the raw materials (e.g., if of biological origin and whether they can be considered growth promoting) and their use in the respective process. The relevant chapters and monographs in the Pharmacopeia, the requirements as defined in the marketing authorisation and other regulations should be considered. Raw materials, components and products and their handling should be assessed as part of the CCS. The specifications should be justified.
44	10.3	Should bioburden be tested on each batch of raw material as incoming control AND on the compounding solution in which it is formulated before sterile filtration?	Yes
45	10.6 iii	What does “different lyophilization loads” actually mean? First and last? Different lyophilizers? Worst cases? Does that mean each sample from a different lyophilizer or samples from different batches in the same lyophilizer?	Lyophilization load means loads for each lyophilizer for each batch, if e.g. more than one lyophilizer is used.
46	10.10	How should situations for products with short shelf life be handled when data exceeds the established limits (including OOS for sterility, see 10.) only after product batch certification?	A procedure should be in place in case a post-release OOS should be obtained to inform physicians, patient and health authorities, to assess the risk for the patient and to define remediation steps as needed. See also Annex 3: 45 and 46

5 Changes to the previous version

- None