SECOND TARGETED STAKEHOLDER CONSULTATION

GMP
Revision on Annex 1
Manufacture of Sterile Products

1. Introduction

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of the Annex 1, it was found necessary to engage with stakeholders in a second targeted consultation on the updated draft guidance, version 12.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

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

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

2. Scope of the consultation

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

2.1. Feedback on the concerns raised by stakeholders		
	Qualification & requalification of cleanroom	from § 4.25 to 4.35
	Handling of water systems	from § 6.7 to 6.15
	Integrity testing of large volume parenteral container	§ 8.21
	Handling of sterilizing filter including pre-use post sterilization integrity testing (Pupsit)	§ 8.88 and 8.95 & 8.96
	Handling of lyophiliser	from § 8.110 to 8.113
	Sterility testing	§ 10.6 & 10.7
2.2. Sections and/or paragraphs which were substantively modified		
	Definition and handling of barriers systems including disinfection/decontamination	from § 4.18 to 4.24
	Handling of gas filters	from § 6.18 to 6.20 and 8.89 & 8.90
	Personnel qualification & gowning	§ 7.5 & 7.6 and from 7.14 to 7.16
	Aseptic production	from § 8.11 to 8.19
	Moist heat sterilisation	from § 8.54 to 8.65
	Personnel monitoring	§ 9.32 & 9.33
	Aseptic process stimulation (APS)	§ 9.34 & 9.40 & 9.47
	Quality control	§ 10.1
2.3. Other significant comments		
	Please avoid re-submitting comments which you already submitted at the first consultation	All document

3. Name and contact details of the reviewing organisation

Please don't add any personal information as the comments might be published

4. Comments ECA and EQPA

Please write your comments using the spreadsheet below

Line number (s)	Comments	Suggested text	Justification
2.1	**Feedback on the concerns raised by stakeholders**		
	from § 4.25 to 4.35		
424 - 427	The text in 4.29 does not precisely and adequately describe what is correctly presented in Table 1.	For cleanroom classification , the airborne particulates should be measured in accordance with ISO 14644 as shown in	Table 1 exactly represents the ISO 14644 requirements and is self-explanatory. The additional text in 4.29 is confusing.
471 (ch. 4.33)	Term “concentration” not correct for microorganisms	The microbial load of the cleanroom	Common terminology should be used in the document.
474 (ch. 4.33)	The term "contamination" is not adequate as some level of microbial load does not have to be regarded as "contamination.	The maximum limits for microbial load.....	Common terminology should be used in the document. Wording should be harmonized.
478 (ch. 4.33)	The term "contamination" is not adequate as some level of microbial load does not have to be regarded as "contamination.	Table 2: Limits for microbial load during qualificaiton	Common terminology should be used in the document. Wording should be harmonized.
494-502 (ch. 4.34)	Rewording suggested - refer to suggested text and justification	The requalification of cleanrooms and clean air equipment should be carried out following defined procedures. The requirement for requalification of cleanroom areas is as follows [Table 3 - excluding airborne microorganisms]. For Grade A & B areas, the maximum time interval for requalification for non-viable airborne particles in operational status is 6 months. For Grade C & D areas, the maximum time interval for requalification is 12 months. All requalification activities may be carried out in operational status for continuously operated cleanrooms. In addition, all data (viable and non-viable airborne particles) obtained from continuous and regular monitoring of manufacturing cleanrooms should be periodically compiled and trended (a least on an annual basis) to provide proof of the intended hygienic status.	The re-qualification should not include viable airborne particles (microorganisms!)but only non-viable. Due to the set requirements in sections 9.5, 9.6 and 9.11 routine monitoring during critical operations should be performed to obtain reliable data from critical zones. When these requirements are fulfilled a requalification activity would not provide additional useful data. All other parameters listed in Table 3 should be included in the requalification activities. Many cleanrooms areoperated continuously, including viable and non-viable airborne particulate monitoring and control. If the re-qualification activities include the need of performing "at rest" monitoring this would not only be providing no additional insight into the status of the cleanroom, but also lead to not justified production interruptions.
503-504	Requirements are evident, but rewording suggested.	Appropriate requalification that considers the above tests should also be carried out following completion of remedial action implemented to rectify an out-of-compliance equipment or facility condition and / or after changes. Examples of	Simplification suggested due to the fact that there is general obligation to investigate out-of-specification situations and changes and identify and perform the necessary subsequent actions.
	from § 6.7 to 6.15	**from § 6.7 to 6.15**	
634 (ch. 6.7)	Modification of wording suggested	microbial contamination and proliferation as well as endotoxins	Microbial contamination and proliferation are independent events. For water quality endotoxins are specified in Ph. Eur. not pyrogens.
653-655 (ch. 6.11)	Omit sterility requirements in context with WFI (as WFI is not sterile).	Where vent filters are used for WFI storage tanks, those should be hydrophobic bacteria retention filters. Appropriate exchange frequencies should be defined and justified.	Even if generally free from microorganisms water for injection (WFI) is not expected to be a sterile media since e.g. the European Pharmacopoeia requirements for this water quality is to contain less than 10 CFU/100ml for microbial count, and bacterial endotoxin levels less than 0.25 IU/ml. The storage tanks, distribution systems (water piping, loops) and points of use (taps or connections to equipment) for the WFI need to be designed, maintained, controlled and monitored relating to the requirements for the manufacturing operations – and storage tank filters for WFI would not need mandatory sterilization and/or integrity testing.

657-661 (ch. 6.12)	Trends should be taken into consideration!	To minimize the risk of biofilm formation, sterilization or disinfection or regeneration of water systems should be carried out based on Quality Risk Management principles or when microbial counts or other monitoring data show a negative trend. Disinfection of a water system with chemicals should be followed by a monitored rinsing/flushing procedure. Water should be tested after disinfection/regeneration. The results should be approved before the water system is returned to use.	Single events (i.e. exceeded alert levels or action limits) should not automatically render sterilization, disinfection or regeneration of the full water system since the excursion may relate to a single point of use and not be a systemic issue in the water system. The actions taken upon single exceeded limits from water samples should rather correlate to the process risks and risks of usage of water in the manufacturing processes. Also, considerations should be given that hot WFI water loops as such are having a self-sanitizing effect, making a pre-determined schedule for disinfection obsolete. Rinsing/flushing procedures for water systems may not be possible to validate but must be monitored with appropriate testing parameters until specifications are fulfilled.
673	Narrow requirements' applicability for WFI.	iii: for WFI: a sample from the point at the end of the distribution loop each day that the water is uded	The section is applicable for water systems in general, but daily monitoring for PW at the end of the distribution loop is not required since PW is used for less critical applications.
675-679	Common terminology suggested.	Alert limit excursions should be documented and reviewed, and include investigation of system trends to determine whether the excursion is a single (isolated) event or if results are indicative of loss of control or system deterioration. Action	"Action limit excursion" is the more common term. "Evaluate" suggested because it does not appear feasible to extect that a potential impact of the water - is used for the process - can reliably be "determined"
	§ 8.21	**§ 8.21**	
1016-1024 (ch 8.21)	Specific conditions for widely used plastic LVP containers should be taken into account.	Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. Blow-fill-seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing. For plastic bags this 100% integrity testing could be performed after all parts of the container are fused and before filling and capping. Samples of containers closed by other methods should be taken and checked for integrity using validated methods. The sampling plan and frequency of testing should be based on the knowledge about and experience with the container and closure systems. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.	LVP plastic-bags (one chamber bags and multi chamber bags) can be 100% integrity tested after welding is completed and before bags are finally filled and capped. This should be clarified in the chapter text since there is as of today no suitable technical solution for 100% integrity testing of filled plastic bags commercially available for implementation. The use of the term "scientifically" in this document is not supported as not defined.
	§ 8.88 and 8.95 & 8.96		
1486-1496 (ch. 8.88)	Emphasize necessity of QRM	If the outcome of the respective risk assessment identifies the necessity, the integrity of the sterilized filter assembly should be verified by integrity testing before use, to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. Test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. ~~It is recognized that pre-use post sterilization integrity testing (PUPSIT) may not always be possible after sterilization due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of non-sterility.~~ Points to consider in the risk assessment should include but are not be limited to:	The approach to refer to risk assessments is supported by recently published results: PDA Letter, Jun 15, 2020 by William Peterson, Merck & Co.: "The Use of Scientific Data to Assess and Control Risks Associated with Sterilizing Filtration" In case the suggested deletion of the sentence will not be accepted, the application of single use systems and closed systems using in-line SIP should be considered and added: (e.g. the filtration of very small volumes of solution, single use systems (SUS) or closed system using in-line SIP)

1533 - 1535	Rely on QRM and subsequent validation approach	However, in the event of a failure of the post-use integrity test on the primary filter, a post-use integrity test on the secondary (redundant) filter should be performed, and a risk assessment should be carried out to demonstrated assurance of the batch sterility.	We suggest to leave out the "to determine the acceptability of performing a post-use integrity test on the secondary (redundant) filter". The point in time to perform such consideration is too late: As the process has to be validated (certainly based on QRM considerations!), there is no need to perform an addional risk assessment to find out if the approach was correct.
	from § 8.110 to 8.113		
1660-1663 (ch. 8.112)	Situation is specific for sterile APIs and this should be reflected.	Lyophilizers that are manually loaded or unloaded should normally be sterilized before each load unless otherwise validated. For lyophilizers loaded by automated closed systems or located within systems that exclude direct operator intervention, the frequency of sterilization should be justified and documented as part of the CCS.	Sterilization processes and manufacturing equipment should be handled and maintained relating to process and product risks; the design and operations of processes should be based on Quality Risk Management principles. The lyophilizer use, and the characteristics and risk for the product operated in the lyophilizer, should form the basis for control and monitoring of the lyophilizer, specifically under consideration of producing sterile APIs.
1665-1669 (ch 8.113)	Alignment with the requirements in 8.112 suggested	The integrity of the lyophilizer system should be maintained following sterilization and during use. The filter used to maintain lyophilizer integrity should be sterilized before each batch or campaign and its integrity testing results should be part of the batch certification. The frequency of vacuum/leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.	To align with the requirements in 8.112 campaign manufacturing may be justified and documented as part of the CCS.
1667	The term "batch certification process" encompasses the QP certification responsibilities as per Annex 16.	" and its integrity testing results should be documented in the batch record.	The basis for batch certification is the batch documentation, including successful handling of deviations. We suggest to avoid selecting and emphazising selected requirements out of the entirety of generally applicable requirements.

	§ 10.6 & 10.7	**§ 10.6 & 10.7**	
2294 - 2295	Requirement should be made more specific	For products which have been filled aseptically, samples should include containers filled at the beginning, middle and end of the batch and after any significant intervention that have not been included in the routine APS	APS has to cover known significant interventions. Thus, these interventions do not require additional sampling for sterility testing.
2305-2308 (ch. 10.6)	Delete the "note"	~~Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilized products) then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests.~~	As terminal sterilization processes have to be performed with qualified autoclaves and validated processes, sterility is ensured if the sterilisation process is performed as intended. Nevertheless, measures have to be taken to ensure and verify that all units have been subject the validated sterilsation process (refer to Section 8.43, lines 1147 - 1148), where respctive measures mentioned! Furthermore, it should be acknowleged that sterility testing itself does not add meaningful information regarding sterility of the product; we suggest to reflect this statement in Section 10.5, lines 2285 - 2288 Should our suggestion not be accepted, the term "sub-batch" needs to be defined. As a minimum, the following modification is is proposed: "Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilized products) then sterility samples from each sub-batch should be taken and a sterility test including each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests."
			Reason: For some LVPs there are over 20 separate autoclave loads for one batch from a single set of preparation vessels and where the LVPs are filled in less than 24 hours. With the draft Annex 1 text reading "a sterility test for each sub-batch performed" this would lead to significantly more sterilty tests for terminally sterilized LVPs compared to aseptically processed products and this does not reflect the sterility assurance risks associated with these different processes. In addition: sterility test samples from one batch of 20 autoclave loads with LVPs larger then 100ml would require 10 samples per autoclave load to be tested per Pharmacopoeia requirements which adds up to 200 samples/batch. LVPs can constitute bags filled with more than 2.5 liters of fluids meaning that one set of samples with 200 bags weighs half of a ton (500 kg) which is difficult to manage in the sample handling and testing operations; especially if the sterility test is to be undertaken as safely as possible in a sterility test isolator.
2.2			
	from § 4.18 to 4.24		

327-330 (ch. 4.19)	Omit the term "sterilisation"	The design of the RABS or isolator should take into account all critical factors associated with these technologies including the quality of the air inside and the background environment, the materials and component transfer, the decontamination processes, the risk factors associated with the manufacturing operations and the operations conducted within the critical zone.	The term "sterilisation" should be avoided as the general term "decontamination" is used in the document
332, 333	Rewording suggested with regard to technolgcal progress.	The critical zone of RABS or open isolator used for aseptic process should meet Grade A requirements.	the general requirement for unidirectional airflow in RABS and open isolators may prevent technological progress. Some constructions that minimize the critical zone in RABS and open isolator have not enough space to demonstrate unidirectional airflow. Of course these constructions need HEPA filtered air supply in overpressure and overspill to the surrounding cleanroom area
356-357	Revision suggested because the described requirement cannot be fulfilled in certain situations	... The testing should be performed at defined periods, at a minimum at the beginning and end of each batch or each campaign and should	For campaign manufacturing (as described in ch 8.96) integrity testing of barrier systems and gloves after every batch may not be suitable and/or possible.
360-362 (ch. 4.23)	Omit the term "sterilisation"	RABS gloves used in Grade A zone should be decontaminated before installation and decontaminated prior to each manufacturing campaign.	The term "sterilisation" should be avoided as the general term "decontamination" is used in the document
366-367 (ch. 4.24)	Omit the term "disinfection"	The cleaning process prior to the decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process:	The term "disinfection" should be avoided as the general term "decontamination" is used in the document
371, 372, 373	Precise requirement suggested	Decontamination methods (cleaning and sporicidal disinfection) should be validated and demonstrate reduction by≥ log 3 to < 6 log .	The current wording "free of viable microorganisms", which is not sufficiently specific. "free" in scientific terms should be supported by figures.
	from § 6.18 to 6.20 and 8.89 & 8.90	**from § 6.18 to 6.20 and 8.89 & 8.90**	
1514 - 1515	Similarity to PUPSIT (for product filters) should be implemented	The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly. It is recognized that post-use integrity testing with the filter remaining in the filter assembly may not always be possible due to process constraints. An alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of non-sterility.	The requirements should be similar to the PUPSIT; furthermore - as a more detailed explanation, the following circumstances are very likely: 1) In-situ post use integrity testing is almost physically impossible because of the sequence of moisturizing and drying required for in-situ testing. The surface tension of moistened filter is crucial, will stop further processing and batches will be lost, in example due to not-wetted areas that may cause false integrity test result. 2) Significant uncertainty for developing product test parameters to cover product ranges, filter membrane specifications and all relevant test situations. GMP requirements such as design, qualification, repeatability and reliability will therefore be difficult to meet with in-situ integrity testing. 3) In-situ post use integrity testing will require additional pipeworks which adds dead-spaces/voids which often are challenging to steam sterilize. 4) Significantly reduced production capacity, huge re-buildings, delays and problems. Proposed annex 1 text may affect supply to marked.

1517 - 1521 (ch. 8.90) in context with 1514 . 1515 (8.89)	Revision needed since requirements are not plausible for non-critical air or gas vent filters		The requirement for non-critical gas filters do not appear plausible since a) non-critical equipment does - per definition - not have impact on product quality and safety b) the requirements in the current text of Annex 1 2nd draft are higher than for the critical gas filters. Looking at the title of the section, the difference between critical and non-critical appears even less clear: Filter sterilization of products which cannot be sterilized in their final container Furthermore, the wording in sections 8.89 and 8.90 is not clear regarding air-filters vent-filters gas-filters We assume to understand the difference (gas-filters as overarching term, sub-divided into vent-filters for ventilation, and air or e.g. nitrogen filters for gases that are direct process gases)
	§ 7.5 & 7.6 and from 7.14 to 7.16		
767-768 (ch. 7.6)	Rewording suggested with regard to qualification status	Non-qualified personnel (e.g. building and maintenance contractors and regulatory inspectors) should not enter Grade B cleanrooms or Grade A zones in operation.	Building and maintenance contractors and regulatory inspectors should not be considered unqualified, but non-qualified when it comes to clean room qualification.
823-832	Requirement should be made more specific	Grade A / B aseptic processing: Dedicated garments to be worn under a sterilized suit.(…) For filling of products (Grade A/B or Grade A/C) that are subsequently terminally sterilized, alternative gowning requirements might be acceptable. The rationale should be documented in the CCS	The term "serilized" should be used, not "sterile", as soon as the gowning in contact with the operator it is no longer sterile. When filling products that are are terminally sterilized in a grade A zone with a grade B or C background the requirements are for gowning does not need to comply with the strict aseptic gowning requirements.
	from § 8.11 to 8.19		
950-952	Alignment with the requirements in Table 5 suggested	The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items and ~~the preparation and~~ filling of the sterile product should be treated as an aseptic process and performed in a Grade A zone with a Grade B background.	Line 950 - 952 may be misinterpreted that preperation of sterile products should be performed in Grade A with Grade B background. This is in conflict with table 5. If this "preparation" refers to preparation of sterile products that cannot be sterile filtered or terminally sterilized after preparation, the sentence is not clearly formulated.
	from § 8.54 to 8.65		
1230-1233 (ch. 8.55)	Reference to risk based approach suggested	Suggested text: "Each item sterilized should be inspected for damage, packaging material integrity and moisture on removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed when risk based defined limits are exceeded."	A packaged and sterilized item not passing the seal and package integrity inspection prior to use should not automatically require a full investigation. The sterilized item would only be used in manufacturing if the sterile package is integer. As such a damaged package would not pose a hygienic risk to the operations and would not need to be investigated, unless an adverse trend of defect packages is obvious.
1230-1231 (ch. 8.55)	Include more aspects for evaluation	For porous cycles (hard goods) the critical process parameters should be used to monitor the process.	Critical process parameters might be not only time, temperature and pressure.

1239-1240 (ch. 8.57)	Requirement should be made more specific	Validation of porous cycles should include a determination of equilibration time, exposure time, pressure and temperature and maximum temperature range during exposure.	During validation the critical process parameters are experimentally determined and the calculation of the correlation of pressure and temperature is not necessary.
	§ 9.34 & 9.40 & 9.47		
2162 - 2166	Requirement should be made more specific	Process simulation tests should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in. Process simulations should also be performed after any significant modification to operational practices, facilities, services or equipment (e.g. modification to the HVAC system, equipment, major facility shut down, changes to process, number of shifts and numbers of personnel etc.).	The proposed wording clearly distinguishes the requirement of three consecutive satifactory APS runs for initial validation from modifications or periodic revalidation where the appropriate number of APS may be based on a risk assessment.
2225 - 2227	Rewording suggested with regard to number of sucessful successful, consecutive repeat media fills	A sufficient number of successful, consecutive repeat media fills should be conducted in order to demonstrate that the process has been returned to a state of control. The number of consecutive repeat media fills should be scientifically justified and based principles of QRM. Typically, a minimum of 3 should be conducted when root causes are not identified, and objective justification cannot be developed.	The wording of the actual draft may lead to interpretation that every single contaminated unit in an aseptic process simulation - irrespective of the media fill size and the outcome of the investigation and root cause analysis - results in the requirement to run three repeat media fills. This does not correspond with concept of Quality Risk Management that should be applied to determine the appropriate number of repeat media fills.
2.3	**Other significant comments**		
16 - 19	Provide broader room for adequate approaches that come via technogical improvement and progress	QRM applies to this document in its entirety and will not be referred to in specific paragraphs. ~~Where specific limits or frequencies are written, these should be considered as a minimum requirement. They are stated due to regulatory historical experience of issues that have previously been identified and have impacted the safety of patients.~~	QRM as a general obigation requires to adequately consider existing guidelines, historical data and experience. With technogical improvement and progress, new and additional requirements may require consideration and may need to be taken into account. Having QRM as the overall concept and narrowing this with the next sentence does not appear feasible.
1561-1563 (ch. 8.97)	Presicion suggested due to specific technological situation	All such containers are considered to be closed through sealing by fusion and, as such, fall under the requirement to perform adequate integrity testing (refer to paragraph 8.21).	Replace “100 %” by “adequate” as 100 % integrity testing is not possible in all cases for flexible bags.
1556 - 1563	Presicion suggested due to specific technological situation	8.97 Form-Fill-Seal (FFS) units include blow moulding from thermoforming from thermoplastic film, typically known as Vertical-Form-Fill-Seal (VFFS). VFFS process is an automated filling process, typically for terminally sterilized products, that may utilize a single or dual web system which constructs the primary container out of a flat roll of thermoplastic film while simultaneously filling the formed bags with product and sealing the filled bags in a continuous process. Formed bags containers are considered to be closed through sealing by fusion and, as such, fall under the requirement to perform 100% integrity testing (refer to paragraph 8.21).	Keep separate section for VFFS since the next section is BFS. Adds confusion to what is needed and what can be supported by BFS

1609-1613	Presicion suggested due to specific technological situation	For shuttle type equipment used for aseptic filling, the area between parison cutting and mould sealing **(critical zone)** should be covered by a flow of filtered air to provide Grade A **viable air** conditions at the critical zone.	Filling environment is not defined. It is better to use Critical Zone for the wording
1609	Presicion suggested due to specific technological situation	For shuttle type include (open parison type)…	Align nomenclature with PDA Technical Report No. 77, The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology
1611-1612 (ch. 8.103)	Presicion suggested due to specific technological situation	The equipment should be installed in at least a Grade C environment with adequate Grade clothing used.	The clothing used should be adequate for Grade C environment. For BFS technology, it has been proven that A/B gowning is not required.
1615-1618	The original text does not sufficiently cover the specific technologocal conditions: 8.104 For rotary-type equipment, used for aseptic filling, the filling environment should be designed to meet Grade A conditions. Other sterility assurance controls such as monitoring of critical parameters and alarms during each batch and parison support filter integrity testing should be considered	For rotary-type equipment, used for aseptic filling, Air in contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container should undergo sterile filtration. It is normally not possible to perform environmental monitoring within the parison. The equipment should be installed in at least a Grade C environment, provided that Grade A/B clothing is used	The rotary machine types uses sterile filtered, which creates the containers and are in contact with the inner surface. This is the same as for shuttle machine as stated in 8.102. Therefore the same wording should be used here. This is in line with the PDA Technical Report 77 Page 22 6.8.8. There is missing a definition for the room classification and gowning, which is the same as for shuttle machines (see 8.102)
1627-1628	The original text does not sufficiently cover the specific technologocal conditions: The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 and 8.4	The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 ~~and 8.4~~	8.4 is not applicable for BFS as it is an advanced filling technology. Short exposure time of open containers in shuttle machines, no open containers in rotary-type machines
2066	Presicion suggested due to specific technological situation	Proposed change, add follwoing sentence: "A truncated cycle duration during the process simulation procedure is acceptable if adequate risk based assessed."	Process simulation test for lyophilized products should not include the requirement of lyophilization cycle duration if in-process controls confirm a closed system during the freeze-drying process.
Entire Document	Guideline is not precise regarding the word "sterile" and "sterilzed"	Example Lines 825/836 A sterile face mask and sterile eye coverings (e.g. goggles)	Both items shall be provided as sterile equipment, but as soon as operators wear them, they are not longer sterile. However, it is a generally accepted requirement that these items should be provided "sterilized".
Entire Document	Avoid the term "organisms" when specific reference to "microorganisms" is made	Microorganism(s)	Align terminology with other guidelines and Pharmacopoeia
Entire Document	Align terminology with other guidelines and Pharmacopoeia	Microbial quality ~~microbial contamination~~	"Microbiological quality" is a more neutral term. Not every microorganism should be regarded as a contamination.
Entire Document	Avoid the work "breaches" and align terminology with other guidelines	Excursion(s)	Align terminology with other guidelines
Entire Document	Avoid the term "lots"; align terminology with other guidelines and Pharmacopoeia	Batch(es)	Align terminology with other guidelines and Pharmacopoeia: If both terms are used in the same document, it should at least be clear if there is a difference and what the difference between the terms is.

ECA and EQPA
20.07.2020