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

Comments from:

Name of organisation or individual
ECA – European Compliance Academy

1. General comments

	General comment (if any)
	From a syntax perspective, it is noted that the guidance lacks homogeneity which might lead to confusion and misinterpretation. It is recommended to revise the entire document for consistency and accuracy of wordings and definitions.
	The Glossary (Lines 2011 ff) requires revision. Apparently, definitions have been adopted from US-FDA "Aseptic Guide" with the consequence that the terms used in the draft of Annex 1 are - defined in the glossary, but not used in Annex 1 draft (e.g. *alert level* is defined, *alert limit* is used in the text. - defined in the glossary, but not used in the defined meaning - Important terms, which are used in Annex 1 draft, are not defined in the glossary (e.g. SIP)
	QRM should be in the glossary. In the document, it is not used in an unambiguous way.
	Although Annex 1 intends to provide *"guidance that should be used for all sterile medicinal products and sterile active substances"* (Lines 12 and 13), it does not give any guidance with regard to APS for sterile APIs.
	The document should be revised to ensure it is written in "clear and unambiguous language" and "brief, concise and clear", to encourage reading, avoid misunderstanding and ascertain that the document can easily be understood, also by non-native speakers - we are the majority! (Quotes are written in *italics)* Examples for unclear wording and definitions: Line 208: *quality unit* - this term is not used in any other of the EU-GMP-Guidance documents (it more US-FDA terminology) Lines 223 – 225 – some quite unusual words: *report any specific health conditions or ailments which may cause the shedding of abnormal numbers or types of contaminants and therefore preclude clean room access* Lines 2011 – 2251: The Glossary explains and defines words and terms that are used in the text. However, apparently sometimes with a different meaning, and are not used in the text at all. Relevant terms, for which one would expect a definition, are not mentioned (e.g. SIP, Sanitization) The same word / term should be used when something has the same meaning, respectively different words / terms, if the meaning is different; examples, where it is not clear: – *Workers – operators – personnel* – *Contamination – microbial and other contamination – microbial, pyrogen and particulate contamination* – *Disinfection, decontamination, bio-decontamination, sterilization* – *SIP* o Line 720: *Steam-In-Place (SIP)* o Line 809: *SIP* o Line 1111: *Steam-In-Place (SIP)* o Line 1145: *Sterilization in Place (SIP)* It is not clear, if the term *manufacturing* includes *packaging*, e.g.: Line 38: *manufacturing, packaging and distribution processes* Terminology for **the products** covered by this document is not consistent, for clarity and easy understanding, it should be harmonized; e.g.: Line 8: *sterile medicinal products ….. (sterile active substance through finished dosage form)* Line 15: *final product* Line 32: *the product* Line 37: *sterile products* Line 136: *sterile manufactured product* Line 142: *product* Line 159: *sterile medicines* Line 161: *sterile dosage forms* Line 1186: *finished materials or APIs* Linr 1863: *sterile active substances* Line 2073: *drug products*

Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
15	Comment: final product to be regarded as final drug product, there may be low bioburden intermediate products Proposed Change: …is prevented in the final drug product.
19	Proposed Change: …gowning, performed according to QRM principles may be used…
30	Rationale: “optimized” is not a scientific or GMP term Proposed Change: delete optimized
37	Comment: The personnel should have a specific focus on aseptic manipulation and protection of the sterile product. Proposed change (if any): suggest adding the sentence “a specific focus on the principle of aseptic manipulation and in the protection....”
38	Rationale: this is regulated in GDP Guidelines Proposed change: delete “distribution”
40 and 43	Comment: It is no specified that cloths for Grade A and B must be sterilized Proposed change (if any): Cloth for Grade A and B must be sterilized; Googles and mouth covers must be used to prevent any skin exposure to the environment.
52 to 54	Comment: The sentence structure is leading to misunderstanding: The effectiveness of the contamination control strategy is demonstrated through efficient contamination control procedure, monitoring measure, and control. The control should include historical data review, trending, and periodic audit of the operators/systems practices versus the program implemented. Finally, the term “strategy” should be replaced by “program” which includes the process in place, the monitoring and the strategy and the sentence review as follow: Proposed change (if any):” A contamination control program (including contamination control procedures, monitoring, and control) should be implemented across the facility in order to assess the effectiveness of the contaminations procedure in place and confirm through risk-based assessment that the monitoring measures/frequency and control in place are effective.”
62	Comment: Sterility Testing of disinfectants used in grade A and B areas. It is not clear which tests and how frequently are required to ensure disinfectants are sterile prior to use Proposed change (if any): Disinfectants and detergents used in Grad A and B areas should be free from microorganisms prior to use, to prevent contamination of the treated surface. Their sterilization process must be validated. Bioboad-Determination should be made on every lot at least once per week with an action level of 1 CFU/100ml, Sampling should be performed directly from the container in which the disinfectant is used.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Line 93-95	….to a standard that will not add significant risk of contamination…. → specify what "significant risk" means in this context. Does it means risk to a certain degree is acceptable or preventive maintenance should be applied as a precautionary measure to reduce risk and not to add a risk….
69-107	Comment: The control strategy is suggested to include a number of listed elements. These elements are a mixture of important and critical items within various systems and subsystems. The verbiage does not indicated which if any are absolutely necessary and which are beneficially advantageous but not absolutely necessary. It is recommended that the verbiage is amended to reflect systems and subsystems, specific elements therein and if these are mandatory. Proposed change (if any): ~~Elements to be considered within such a documented contamination control strategy should include (but not be limited to):~~ ~~a) Design of both the plant and process.~~ ~~b) Equipment and facilities.~~ ~~c) Personnel.~~ ~~d) Utilities.~~ ~~e) Raw Materials Control – including in-process controls.~~ ~~f) Product containers and closures.~~ ~~g) Vendor approval – such as key component suppliers, sterilization of components and single-use systems, and services.~~ ~~h) For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly.~~ ~~i) Process risk assessment.~~ ~~j) Process validation.~~ ~~k) Preventative maintenance – maintaining equipment and premises (planned and unplanned maintenance) to a standard that will not add significant risk of contamination.~~ ~~l) Cleaning and disinfection.~~ ~~m) Monitoring systems – including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination.~~ ~~n) Prevention – Trending, investigations, corrective and preventive actions (CAPA), root cause determination and the need for more robust investigational tools.~~ o) Continuous improvement based on information from the above systems. Quality systems and respective elements that must be considered within the control strategy are tabulated below: **Quality System** — **System Content (includes but not limited to)** Facility — Design, traffic flows, utilities, maintenance preventative and repair, cleaning, disinfection, monitoring systems Manufacturing Process — Design, equipment, in-process controls, in-process tests Personnel — Training, certification, garbing,

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	Procedures — Vendor approval, out sourcing, risk assessments, trending, analysis, investigational tools, CAPA, continuous improvement Product — Raw materials, in-process tests, end product tests, containers, closures
113	Comment: Integrity Test of filters after sterilization and pre-use increases in many cases the risk of a product contamination due to further (aseptic) handling with the filter during filter testing prior to fill. Proposed change (if any): Timepoint of Filter integrity testing of sterile filters prior to fill should be performed based on a risk assessment
130	Rationale: visual inspection is a probabilistic process <USP 1790>; in line with EP<parenteralia> wording; a reference to the applicable Pharmacopoeias should be made Proposed Change: .. all final products are free from microbial and other contamination and essentially free of particulate matter
Line 190 Line 199-200	Comment: line 190 is in contradiction with line 199. Please precise whether hands and arms and chests are considered *key* or *additional*. Proposed Change: Line 190 : key locations e.g. hands arms and chest (comma missing) Line 199 : additional locations such as arms and chest
197	Comment: There is requirement is for personnel working in an A/B cleanroom for unloading autoclaves, cleaning… Proposed change: ….and aseptic practices according to their actual tasks (in general specified in job descriptions).
200,201	Comment: there is requirement is for personnel working in an A/B cleanroom for unloading autoclaves, cleaning, learning which is not directly involved in aseptic filling processes but needs access to A/B. Of course they need to pass gowning qualification but no APS Proposed change: delete- and have participated in a successful aseptic process simulation test, during which they have performed their normal duties,…
Line 202	Comment: It is not clear what “normal”duties means Proposed change (if any): replace the word “normal” with “routine”
Line 206	Comment: The term “critical” intervention” needs to be specified. Even routine interventions can be critical with respect to product sterility Proposed change (if any): Routine and critical interventions should be pre-defined using risk management principles.
203-206	Comment:

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	Personnel in the Grade A/B area have different risk profiles (e.g. personnel conducting critical interventions as compared to a quality observer that is not directly participating in manufacturing processes). Proposed change (if any): The microbial monitoring of personnel in the grade A/B area should be performed to assess their aseptic behaviour. This monitoring should take place immediately after completion of a critical intervention and upon each exit from the cleanroom for personnel conducting critical interventions.
207	Comment: "monitoring" appears sufficient, there is an obligation to implement a meaningful program and "continuous monitoring" may implicate use of settling plates everywhere, which is neither possible nor required. Proposed change: delete "ongoing and continuous"
230-234	Comment: Requirement needs to be assessed, especially for staff engaged in microlab and inoculum (biologic API production) Proposed change: replace 233 "sterile product areas" by "A/B-area".
236-237	Comment: Smart phones and tablets are essential communication tools also in CNC, D and C areas. Proposed change: Wristwatches, make-up and jewellery should not be allowed in clean areas. Items required for the actual operations and adequate for the respective area may be brought into the clean areas.
244	Comment: Both conditions should apply. Proposed change (if any): "usable garments should be replace based at a set frequency determined by qualification and / or if damage is identified"
254	Comment: shoes may need to be dedicated. Proposed change: delete "appropriately disinfected shoes"; add "appropriately clean shoes, which may be dedicated."
251 – 275	Comment: Presenting the requirements in a table would be easier to understand. Proposed change (if any):
276-279	Comment: Persons who enter clean areas (CNC, D and C) eg,. Visitors, should be allowed to gown up from outdoor clothing in multiple layers of appropriate overalls/shoe covers/hair/mouth covers. QRM should be applied to define the adequate clothing Proposed change: add …or multiple layers of appropriate overalls/shoe covers/hair covers.. Delete: Where clothing is reused this should be considered as part of the qualification.
Line 277	Comment: Dedicated socks? Is this necessary? It should be based on QRM

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	Proposed change (if any): delete “including dedicated socks”
Section 5	Comment: Suggest to rearrange the section into logical sequence with 3 subsections: have the A, B, C, D physical separation first, then pressure cascade, then unidirectional airflow….
351	Comment: The contaminants should not be limited to fibres. Proposed change: Materials liable to generate fibres and other contaminants should not be permitted in: A/B or in grade C or D where open product / containers / equipment is exposed to the environment.
Line 365- 375	Comment: Airlocks should be flushed effectively with filtered air. The term “filtered air” does not describe the requirement precisely. Proposed change (if any): Airlocks should be flushed effectively with air of the respective clean room grade.
384	Comment: The continuity of grade A should not be limited to transfer from B to A. The continuity of grade A can be maintained only if the process prior the grade A (before going into the RABS/Isolator) or when the product is in direct contact with a Grade A environment (during process or storage in its final container). The suggestion is to add sentence to the line 384 Proposed change (if any): “the continuity of grade A must be ensured at every area transfer when the material will be used in a grade A or will be used in for aseptic manipulation. Therefore, the wrapping number or type should be adapted to always maintained the continuity grade A of the material, the intermediate or product wrapped.”
390 – 392	Comment: The continuity of the highest required clean room grade should be maintained throughout any transport across different areas. Thus, ii) and iii) should not be restricted to A / B. We suggest iii should be broadened. “iii. The movement of material from clean not classified (CNC) to grade C should be based on QRM principles, with cleaning and disinfection commensurate with the risk.” Proposed change: iii. The movement of material from clean no-nclassified (CNC) to any higher clean room grade should be based on QRM principles, with cleaning and disinfection commensurate with the risk, ensuring that the continuity of the desired final grade is maintained (e.g. continuity of grade A as described in ii)).
412-421	Comment: “Air flow patterns should be visualised in grade A/B areas to evaluate if airflow is unidirectional.” could be interpreted that unidirectional air flow is required in Grade B areas. Air flow in Grade A should be unidirectional. Grade B typically has turbulent flow. An important consideration for air flow visualization studies is to ensure that there is no air ingress from grade B areas to grade A areas. Proposed change (if any):

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	Air flow patterns should be visualised to evaluate if airflow is unidirectional in grade A and there is no air ingress from grade B to grade A. (Note: refer to clause 5.17 regarding isolators)
Line 425-426	Comment: “The pressure differences should be recorded regularly or otherwise documented” – it is not clear what the meaning of “otherwise documented” is. Proposed change (if any): delete “regularly recorded or otherwise”, it should be “documented”
430/431	Comment: Camera supervision needs to be aligned with requirements of privacy protection regulations; thus it may not be a general requirement
433-439	Comment: Some product-contacting equipment is already located in the isolator prior to decontamination as transfer of this equipment as already sterilized equipment is quite often due to size & weight not possible. In this case decontamination with respective validation of SALl of 10E-6 and supportive data that all relevant surfaces of the equipment are reached by the decontaminating agent should be acceptable. Proposed change (if any): 5.15 Isolator or Restricted Access Barrier System (RABS) technologies, and the associated processes, should be designed so as to provide maximum protection of the grade A environment. The transfer of materials into and out of the RABS or isolator is one of the greatest potential sources of contamination and therefore any of such activity that potentially compromise the sterility assurance of the critical zone should be assessed and controls applied if they cannot be eliminated. Make a new comment – no sterilization of the isolator, but bio-decontamination
439	Comment: The isolator as such is not sterilized, but disinfected. Proposed Change: … following disinfection ~~sterilisation~~ should be minimized
Line 446	Comment: "risk factors": What is meant by risk factors? the phrase is used once in the document. Introducing a new term only adds confusion if there is not a specific point.
450-451	Comment: Turbulent air flow is seen on occasion in RABS as well as closed isolators. Examples where turbulent airflow can be observed is near large pieces of equipment, such as stopper bowls, or ~~as well as~~ mouse holes in the RABS and open isolators. Proposed change (if any): Under certain circumstances turbulent airflow in Isolator or RABS may be justified ~~in a closed isolator~~ when proven to have no negative impact on the product. Delete the word “closed”
453-456	Comment: Disagree on wording Proposed change (if any): The sentence construction is not correct; probably the "and" before "studies" should be removed
460	Comment: the term “decontamination” used is not adapted based on the definition proposed in the general comment. A sporicidal agent is capable of reducing micro-organisms (cfr.: definitions proposed in the general comment). The goal of a sporicidal agent is to reduce microbial contaminations. As a matter of fat,

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	a sporicidal agent does not generally contain surfactants in their formulation, therefore, no cleaning action is possible. Only mechanical operations could be achieved when the sporicidal agent is applied using wipes. The term disinfection (reducing based on a defined log reduction) should be used. Finally, the term propose is in line with the following sentence used in line 462. Proposed change (if any): “For open, positive pressure isolators or closed isolators with disinfection by a sporicidal agent, ...”
469;470	Comment: production isolator filling lines in grade C or D require continuous (vials) or discontinuous introduction of items. This is performed using VHP airlocks for sterilized equipment in overwrap, dry heat tunnel or autoclaved RTP containers Proposed Change: delete lines 469/470
470-478	Comment: When the isolator is closed and has been decontaminated, only visual glove integrity testing can be performed. Performing mechanical and physical testing might the risk of breaking the aseptic status of the line. The principles of QRM should be applied Proposed change (if any): 5.21 Glove systems, as well as other parts of an isolator, are constructed of various materials that can be prone to puncture and leakage. The materials used shall be demonstrated to have good mechanical and chemical resistance. Integrity testing of the barrier systems and leak testing of the isolator and the glove system should be performed using visual, mechanical and physical methods. They should be performed at defined periods; physical methods are used once the isolator is not decontaminated; visual and mechanical methods are used at a minimum of the beginning and end of each batch, and following any intervention that may affect the integrity of the unit.
475	Comment: what is meant by mechanical integrity testing? Proposed Change: delete “mechanical”
477	Comment: During aseptic processing gloves cannot be tested. Proposed Change: delete: … and following any intervention trhat may affect integrity of the unit Add: ..according to QRM.
480	Comment: same as the 460. Proposed change (if any): replace “decontamination” by “cleaning and disinfection”.
505/Tab1	Comment :ISO classification for in operation/at rest : not correct for B and C (should be reversed)
550	Comment: if the excepted results is 0 then why put 1 in the table. This lead to confusion. Proposed change (if any): replace “1” by “0”
560/561	Comment: In practice requalification of cleanrooms cannot be scheduled at an exact monthly interval. Scheduling needs an interval. Proposed Change: A/B: 6 months plus/minus 2 months for grades C and D 12 months plus/minus 2 months should
567	Comment: The section “disinfection” should be replaced by “cleaning and disinfection”

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570	Comment: A separate cleaning should not be mandatory prior each disinfection. Current disinfectants on the market are formulated with surfactants that have the capability to clean and disinfect in a one step. However, it should be stated that if the surface to be cleaned and disinfected contain high level of soils then a cleaning step prior disinfecting may be needed. The use of a detergent (for the cleaning step) should be defined based on the soil level of clean-rooms surfaces, the composition and effectiveness of the disinfectants to clean the soil, e.g., a surfactant in the composition will help to clean and disinfect. Finally, after the use of a detergent, a rinse step is needed to avoid residue build-up or possible interaction with the disinfectant. Proposed change (if any): Remove the sentence between brackets.
571	Comment: Disinfectant use is unlikely to lead to microbial resistance development. The idea behind disinfectant rotation is to cover the largest microbial spectrum. The disinfectant rotation frequency should be based on the historical EM data trending over time and the disinfectants' efficacy profile. Therefore, the obligation for disinfectant rotation is not scientifically supported: The number of disinfectants to be used along with a sporicidal agent, their rotation, and program frequency should be justified based on the microbial risk assessment results, disinfectant and sporicide microbial efficacy profiles, area classification, and review of the historical EM data. The environmental control program, including EM program, cleaning and disinfection program, qualification and periodic re-testing of the disinfectants should be looked at as a lifecycle approach (feedback loop). As a matter of fact, the historical EM data review, Figure 1, is one of the triggers to adapt or improve the cleaning and disinfection program and confirm that the disinfectant and sporicide microbial efficacy profile and spectrum is adequate. Finally, periodic historical EM data review and analysis must be performed to: - Confirm the absence of the increase in excursions from the previous historical EM data analysis. - Identify the specific re-occurrence of trend or adverse events (e.g., the recurring deviation with the same microorganism or recurring excursion on the same sampling position). - Identify specific worst-case microorganism. - Categorize the source of isolate and contamination factors. - Confirm the absence of a high occurrence of microorganisms of concern or microorganisms considered as objectionable or those under official scrutiny, e.g., Burkholderia cepacia. Figure 1: Confirm effectiveness of the cleaning and disinfection program through fact and data

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	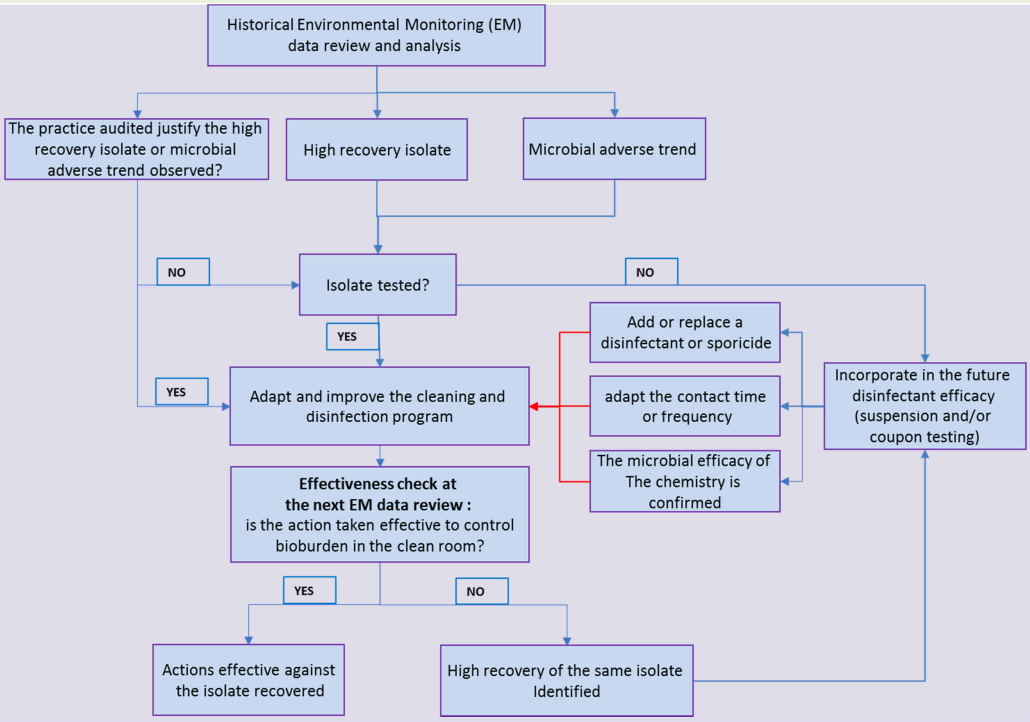 Source used: Japan (JP) Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing (2006): United States Food and Drug Administration (US FDA) guidance on aseptic manufacturing (2004): Sutton, S. "Disinfectant Rotation a Microbiologists View" Cleanrooms, 2005, access on May 25, 2017 at: https://www.cemag.us/article/2005/07/disinfectant-rotation-microbiologists-view United States Pharmacopeia (USP) <1072> El Azab Walid, Cleaning, and disinfection program part of the lifecycle approach: a risk-based rather arbitrarily imposed approach, GMP Journal, edition January/February 2018 Proposed change (if any): "The number of disinfectants to be used along with a sporicidal agent, their rotation, and program frequency should be justified based on the microbial risk assessment results, disinfectant and sporicide microbial efficacy profiles, area classification, and review of the historical Environmental Monitoring data."
576	Comment: Disinfectant use is unlikely to lead to microbial resistance development. Sutton concludes that "the probable scenario for selection of a development of resistant variant would require exposure of an extremely large number of cells (in excess of 1,000,000 CFU) to a low level of the toxic chemical." (13). Such circumstances should not arise in a typical clean-room. Also, Sutton states that "selection of mutants that are resistant to in-use levels of disinfectants has not been shown to happen in cleanroom settings. Literature reports of resistance to in-use levels are restricted to descriptions of survival of specific microorganisms in contaminated solutions". Proposed change (if any): "effectiveness of the disinfection program and to detect the presence of resistant and/or spore forming strains"
578-580	Comment:

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	Containers for detergents and disinfectants used in Grade A and B should be sterile (not only be cleaned) Proposed change (if any): 5.32 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned and sterilized containers and should only be stored for defined periods. Disinfectants and detergents used in grade A and B areas should be sterile prior to use.
577	Comment: The “cleaning program” term is not appropriate because the goal is to remove the residue of disinfectant or detergent. Therefore, we suggest using the term “rinsing program”. This term is widely used in the pharmaceutical literature such as PA technical report 70, USP 1072, Proposed change (if any): “rinsing program should be effective in the removal of disinfectant and detergent (if used) residues.”
588-589	Comment: Distinction should be made between ‘contamination’ - microorganisms, pyrogens and particulates which represent a direct hazard and risk to product quality and microorganisms, pyrogens and particulates which are not hazards to product quality. Proposed change (if any): Fumigation or vapour disinfection of clean areas such as Vapour Hydrogen Peroxide (VHP) may be useful for reducing ~~microbiological contamination~~the microbial load in difficult to access locations.
597/598	Proposed Change: …….. Alarms related to CPPs should be …
619	Comment: Product fluid paths can be sterilized-in-place or aseptically assembled after autoclaving parts in a sealed container. Stopper hopper and stopper rails are often too large for autoclaving in a sealed bag or container and subsequent aseptic assembly. For conventional clean rooms and open RABS systems these components are autoclaved and transferred to the filling line with appropriate coverings and assembled with aseptic precaution. For isolators after autoclaving and assembly there is a subsequent VHP decontamination possible. Thus, the strict requirement of sterility of all critical surfaces should be avoided. Proposed Change: … All critical surfaces that come into direct contact with sterile materials should~~.~~ have been sterilized~~be sterile~~.
667-669	Distinction should be made between ‘contamination’ - microorganisms, pyrogens and particulates which represent a direct hazard and risk to product quality and microorganisms, pyrogens and particulates which are not hazards to product quality. Proposed change (if any): Water treatment plants and distribution systems should be designed, constructed and maintained to minimize the risk of microbial ~~contamination~~ ingress and proliferation so as to ensure a reliable source of water of an appropriate quality.
Line 688-689	Comment: *7.12 – Where WFI storage tanks are equipped…tested before and after use…. Should precise whether it is use of tanks or use of filter* WFI buld is not claimed as sterile according to Pharm. Eur. Sterilization of vent filters is best practice but depends on risk based approach. Due to the fact that vent filters in water systems are heated anyway to prevent condensation conditions are present so that microbial growth is unlikely. Also filter integrity test

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	prior to use should be discussed as risk based approach. Proposed changes: Where WFI storage tanks are equipped…tested before and after use…of the filter should be performed, considering the individual conditions and the QRM principles.
691 693 695	Comment: Effective cleaning and sanitization or cleaning and disinfection or cleaning and sterilization process must be performed to prevent formation of biofilm. Only a disinfection or sterilization process by killing microorganisms will not be efficient to proactively avoid biofilm formation. The residue of the dead cell will increase the rugosity of the surface in the piping allowing planktonic cell to fix and use dead cell as food to develop a new biofilm. Proposed change (if any): "7.13 To prevent the formation of biofilms, cleaning followed by a sanitization or disinfection or sterilization or regeneration of 692 water systems should be carried out according to a predetermined schedule. When 693 microbial counts exceed action and alert limits. Sanitization or disinfection step of a water system with chemicals should be followed by a validated rinsing procedure. Water should be analyze after the cleaning and sanitization or cleaning and disinfection or regeneration…"
Line 703	Replace "Include all outlets" by" include all **critical** outlets"
Line 704-706	Comment: System design should ensure that the distribution system is always in a good state (positive pressure differential, no backflow). Can these elements be considered a surrogate to the worst case sample point?
Line 705	Comment: A water system could be used many times per day, it seems overkill to need to take a sample each time it is used. Proposed change (if any): Revise to have a time boundary.
Line 715-716	Comment: For pure steam generation, purified water with a low level of endotoxin should be used. As the pharmacopeia monographs do not require endotoxin testing or limits for PW, the expectation is not clear. Proposed: Delete "low level of endotoxin" or otherwise provide clear guidance.
735	Proposed Change: add …prevention of backflow or other precautions (QRM) when… Rationale : there are vacuum transportation systems for vials and stoppers in filling lines- the vacuum there is broken using the HEPA filtered air in class A
740-743	Comment: Clarification is requested if this requirement refers to leakage inside a room. It is unclear from the guidance which systems this applies to. Is it meant for Lyo's or BFS? To chilled water systems for formulation jackets? Depending on what systems this applies to, it is unlikely that leak detection and disinfection of cooling systems such as chilled water is feasible. Proposed change (if any): 7.21 Major items of equipment associated with hydraulic and cooling systems, ***such as stationary and portable chillers and lifts***, should, where possible, be located outside the filling room. Where they are located inside the filling room there should be appropriate controls to contain any spillage and/or cross contamination associated with the hydraulics of cooling system fluids
745/746	Proposed Change: must be detectable or excluded by construction principles

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745-746	Comment: Clarification is requested if the term 'any leaks' ~~this requirement~~ refers to (a) leaks which directly enter the product contact surfaces or wetted path or (b) leaks which present a contamination hazard in the facility. The proposed change is worded to try to reflect the leak described in (a). ~~cross contamination potential. what is criteria for flow? Is there a concern for chilled water/glycol systems to maintain flow?~~ Proposed change (if any): 7.22 Any leaks from the cooling system which have the potential to directly contaminate product must be detectable (i.e. an indication system for leakage). In addition, there must be adequate cooling flow within the system.
751/752	Comment : cleaning/disinfection of both vacuum and cooling systems is technically not suitable for inline vacuum systems or heat exchangers used for cooling. Proposed Change: delete 7.24
751-752	Comment: This requirement appears to be specific to lyophilisation and should be moved to that section of Annex 1. Proposed change (if any): There should be periodic cleaning/disinfection of both the vacuum system and cooling Systems (e.g. lyo cabinet).
751 752	Comment: Why cooling system not in direct contact with the product should be disinfected. The term disinfection is not adequately used in the document (see definition proposed in the general comment section). Cleaning of the cooling system should be sufficient if needed. This should be part of the preventive maintenance program. A sanitization should be required if the Environmental monitoring detects microorganism of a cooling system origin. Proposed change (if any): "751 7.24 There should be periodic cleaning of both the vacuum system and cooling 752 systems. A sanitization may be needed if microorganism from cooling or vacuum system are identified in the environmental monitoring data"
758-764	Comment: Distinction should be made between 'contamination' - microorganisms, pyrogens and particulates which represent a direct hazard and risk to product quality and microorganisms, pyrogens and particulates which are not hazards to product quality. Proposed change (if any): Preparation of components and most products should be done in at least a grade D environment in order to ~~give~~ ensure ~~a~~ low ~~risk of~~ microbial, pyrogen and particulate ~~contamination~~ risks, so that the product is suitable for filtration and sterilization. Where the product is at a high or unusual ~~risk of~~ microbial ~~contamination~~ risks, (for example, because the product actively supports microbial growth and/or must be held for a long periods before sterilisation and/or is not processed mainly in closed vessels), then preparation should be carried out in a grade C environment.
769-773	Comment: Distinction should be made between 'contamination' - microorganisms, pyrogens and particulates which

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	represent a direct hazard and risk to product quality and microorganisms, pyrogens and particulates which are not hazards to product quality. Proposed change (if any): Where the product is at an unusual microbial or particulate ingress risk ~~of contamination~~ from the environment because, for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, or the product is held for extended periods prior to terminal sterilization, then the product should be filled in a grade A zone with at least a grade C background.
782 – 784	Comment: There should be a requirement for the clean room grade, in which weighing operations have to be carried out. Without such requirement, there is continuous discussion about the adequate clean room grade. Proposed change (if any): Add "weighing" under "Grade D"
794-795	Comment: A single control strategy, and an appropriate strategy term is needed which includes and distinguishes between the different approaches to controlling microorganisms, pyrogens and particulates which represent direct hazards to product quality and microorganisms, pyrogens and particulates which do not represent a hazard to product quality. Proposed change (if any): The site's ~~contamination control strategy~~ microbial and particle control startegy should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness.
Line 797	Comment: 'Residual risks should be justified.' Line 148 –150 already describe the risk assessments and residual risk. In order to make the document clean, please remove this sentence. Proposed change (if any): Please remove 'Residual risks should be justified.'
Line 799	Comment: "precautions to minimise microbiological, pyrogen…". Microbiological includes bioburden. Proposed changes: revised by stating "precautions to minimise bioburden, pyrogen and …."
814	Comment: avoid debate of sealing/capping as sterile/clean process due not mentioning this in this table Proposed Change: Table 4: A: change "sealing and capping as an aseptic process" (8.22) C: add " vial capping as a clean process" (8.22) Add A: vial capping as an aseptic process Add C: vial capping as clean process.
814 – 816	Comment: There should be a requirement for the clean room grade, in which weighing operations have to be carried out. Without such requirement, there is continuous discussion about the adequate clean room grade. Proposed change (if any): Add "weighing of materials of solutions to be filtered" under "Grade C"
Line 814 -816	Comment: Table 4: Examples of operations … For Grade B, it states "removal of sealed product from the Grade A zone." Sealing of product may be performed outside of the Critical zone under Grade A air supply (see clause 8.21 and 8.22). The surrounding environment for such activity is typically Grade C or D. Therefore the sealed product would be removed from a Grade C zone, not Grade B. If the product is

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	sealed, then there is no impact to the sterility of the product and it does not need to be removed from the Grade B zone. Proposed change: Remove this example from Grade B operations in Table 4, or provide additional information for what type of process would require removal from the Grade B zone.
852/853	Proposed Change: 8.16 The duration of each aspect of the aseptic manufacturing process should be limited to a defined maximum and validated according to QRM principles, including: Comment: Exposure time of individual sterilized containers or stoppers is not possible to track and trace.
Line 861-862	Comment: In addition to processing time and chemical stability, microbial hold time of the in-process material is critical for API (prior to compounding), compounded DP, and bulk DP prior to sterile filtration. Proposed changes: requiring justification of hold time with respect to microbial quality and performing microbiological testing at the end of hold.
888	Comment: Use of a statistically valid sampling plan for integrity testing results in large numbers of containers to be tested. Proposed change: Delete sentence with "statistical valid sampling plan"
883-890	Comment: Alternate wording will allow for flexibility regarding to justifying the container closure system based on quality by design, end to end process controls, and appropriate testing as defined by QRM principles. Proposed change (if any): Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. Form-Fill-Seal Small Volume Parenteral (SVP) & Large Volume Parenteral (LVP) bags, glass or plastic ampoules, should be subject to 100% integrity ~~testing. Samples of other containers should be checked for integrity utilising validated methods and in accordance with QRM, the frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A statistically valid sampling plan should be utilized.~~ For other containers, closure integrity should be evaluated utilizing QRM methodology taking into consideration knowledge and experience with the closure system to define the controls and test plan. Test methods should be validated. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.
892	Comment: For legacy products transition time required for implementation of testing technology and establishing appropriate limits.
Line 892-893	Comment: Clarification on what constitutes vacuum is required. Products that require only a partial vacuum may not be able to be tested using current available technology due to limits of detection at end of shelf life for maintenance of vacuum levels. Proposed change (if any): Add "For product requiring full vacuum headspace" or where reconstitution time is a critical parameter Containers sealed under Vacuum …..predetermined period and during shelf life: delete *and*
892-893	Comment: Is this testing required even if the vacuum is not for product quality purpose? For example, containers that are at almost atmospheric (i.e slight vacuum that aids in reconstitution of a lyo cake) where accurate vacuum testing may not be feasible.

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	Proposed change (if any): Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate, pre-determined period and during shelf life, if vacuum is required for the purpose of product quality.
895	Comment: For legacy products; a transition period should be granted: Time is required for including shipping /transportation in the CCIT validation.
909-913	Comment: The raised stopper detection limit should be supported by CCIT. Does the CCIT have to be validated? Microbial ingress is stated as a method, but is this testing adequate for this purpose? Proposed change (if any): In the case where capping is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately validated, automated methods for stopper height detection should be in place. ~~Microbial ingress studies (or alternative methods) should be utilized to determine the~~ acceptable stopper height displacement.
928	Comment: appropriate corrective actions could consider total or partial batch rejection, market recall, or re-inspection and eventually release, if root cause of unusual level of defects were caused by non-conformance of the inspection process. Proposed Change: Delete: consideration of partial or the whole rejection of the batch concerned. Add: and appropriate corrections and corrective actions.
Line 929-930	Comment: A defective library should also capture defects that are product specific. Proposed changes: recommend revising the statement to something such as “A defect library should be generated and maintained which captures all known defects from the manufacturing process and from defects which are specific to the product manufactured.”
931 – 932	Comment: a) The phrase is somehow misleading, slight rewording suggested. b) Visual inspection (manual or automated processes) is regarded as a probabilistic process <USP7090>, this means that also critical defects may be found during subsequent sampling as for QC testing or stability testing or 100% inspection for specific country allocation e.g. Japan.. Proposed change: No Critical defects should ~~not~~ be identified during any subsequent sampling of acceptable containers as it indicates a failure of the original inspection process. Identification of containers with critical defects should trigger an investigation.
936	Comment: The meaning of the word “robust” is not clear as any qualification fulfills the requirement of being “robust” Proposed change: Operators performing the inspection should undergo ~~robust~~ visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually.
941	Comment: “operator distractions should be removed” will always be a debate during authority inspections as “distraction” is on individual judgement. Proposed change: Delete: “operator distractions should be removed”
944-946	**Comment 1**: The use of the term “sensitivity” may be mistaken as sensitivity in terms of defect size, i.e.,

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	particulate size or the overall defect rate. The statement should suggest the "detection capability." Otherwise, it may be understood as if the manual inspector can detect 100 micron particulate, the automated inspection should be able to detect 50 micron particulate. Which is a very different statement altogether. Proposed change (if any): A clarification of "sensitivity" is needed here or simply state that automated methods should be equal or better than manual inspection methods. **Comment 2** on sentence "Where automated …. Prior to start up and at regular intervals" Actually, Whole system Checks should follow a schedule of testing at regular intervals. This is to be defined and justified by equipment qualification and should take into consideration specificity of the defects seen in the material being tested.
Line 948-951	Comment: Inconsistent language in this clause. Does "level" also mean "reject rate" or are these two different attributes? The use of defect "level" is also discussed in clause 8.26 (Line 927), and it is not clear if this also can be used synonymously or interchangeably with "reject rate". If reject rate and reject level are synonymous, then clause 8.29 (Lines 949-950) is redundant to clause 8.26 (Lines 922, 926-929) with regard to trending and investigations. Proposed change: please use consistent terminology so as to be clear on the intent. Please remove any redundant text.
973	Comment: need to consider RTU – and SUS -technologies Proposed Change: For finished medicinal products where possible, heat sterilization is the method of choice. For components like rubber stoppers, prefillable syringes and vials in a "ready to use" (RTU) quality and single use systems (SUS 1517) other validated methods of sterilization may be appropriate.
973 - 975	Comment: Specific reference is made to the requirement that the process is in accordance with the registered marketing and manufacturing specifications is made, which is applicable for any and all process parameters, which are part of the marketing authorization. Proposed change: Delete the sentence: ~~Regardless, the sterilization process must be in accordance with the registered marketing and manufacturing specifications.~~
996 997 998	Comment: This requirement "Prior to use of a new batch/lot of BIs, the quality of the batch/lot should be verified by confirming the viable spore count and identity." is not in line with the QRM approach promoted in the recent review of the EU GMPs. The frequency of testing a new batch of BI should be set based on the Quality System (Chapter 1 and Annex 1 additional PQS), the audit system through EU GMP chapter 7 and the QRM results of the supplier and the results risk assessment on the sterility assurance level of the product to assess the frequency of BI batches to be tested versus relying on the supplier CoA. Proposed change (if any): "the quality of the BI batch/lot should be verified by confirming the viable spore count and identity. The frequency of the verification (each new batch/lot or periodically) should based on the

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	supplier history and testing data, the supplier audit and the sterility risk assessment results."
1003 – 1004	Comment: The current wording in the draft Annex 1 is "Seal and packaging integrity should also be inspected immediately prior to use. Any items found not to be fit for purpose should be removed from the manufacturing area and an investigation performed." A packaged and sterilized item not passing the seal and package integrity inspection prior to use should not automatically require an investigation. Even operating with utmost diligence, damaged containers may occur. Of course, depending on the circumstances, e.g. when posing a contamination risk to the operations, further investigation may be required. However, investigations should be performed based on QRM principles. **Proposed change (if any):** "Seal and packaging integrity should also be inspected immediately prior to use. Any items found not to be fit for purpose should be removed from the manufacturing area ~~and an investigation performed..~~"
1021	Comment: It is not possible nor suitable for isolator facilities with grade C or grade D. Proposed Change: delete requirement of storing items sterilized in house in a at least grade B environment.
1029, 1053, 1061, 2100	Comment: Although broadly used, the term "depyrogenation" conveys the wrong impression about the target of the activities. Here, the target is "sterilisation", which is achieved by dry heat treatment that reduces endotoxins by 3 log steps, **while** sterilization is achieved. (Note: It is thus not even a general depyrogenation, but a "3-log-endotoxin reduction"). It is, of course, acknowledged that endotoxins and pyrogens need to be reduced to a level that ensures compliance with the compendial requirements. Thus, this comment does not question the need for "pyrogen-free" / "adequately low endotoxin level" in any way. The terminology is put in question for the following reasons: • "depyrogenation" is only the outcome, when sterilization is performed via dry heat treatment, which is not the only method commonly applied to achieve sterility; other methods are applied e.g. e-beam, irradiation – and these methods do not bring the depyrogenation effect of 3-log-endotoxin reduction) • only glass containers can be depyrogenated via dry heat treatment; i.e. containers of other (plastic) material, which are also broadly accepted and used, cannot undergo this treatment – and they are adequate (regarding pyrogen level and sterility) in spite of this. • if applied in the current sense, the requirement of "depyrogenation via dry heat" is apparently applicable only in case of aseptic manufacturing; i.e. all i.v. products, for which sterility is achieved via terminal sterilization, do not undergo the "depyrogenation via dry heat treatment" (If "depyrogenation" was the major target, the terminally sterilised products would need depyrogenation even more. Other than in aseptic processes, there ARE at least some residuals of microorganisms that remain in the product and could thus form endotoxins – this is not the case for aseptic processes!) • under 8.46 *"When a depyrogenation process is used for any components or product contact equipment, validation studies should be performed to demonstrate that the process will result in a minimum 3 log reduction in endotoxin. There is no additional requirement to demonstrate sterilization in these cases."* There is a clear indication that by determinin 3-log-reduction in endotoxin during the dry heat treatment, there is no requirement to demonstrate sterility, which is considered as an indication of the actual target of the process → sterilisation (demonstrated via 3-log-reduction in endotoxins!)

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	Proposed Change: Adapt the terminology; the sections may be moved to the “dry heat sterilization” section
1028 -1030	Comment: There are many more suitable methods for transfer of materials like e-beam, RTP ports, “no touch” processes, transferring sterilized items packaged with multiple sterile packaging layers or other technologies. Other technologies may arise. These technologies have be assessed according to QRM during facility and process design and are part of the contamination control strategy. Proposed Change: delete 8.42
1035	Comment: there exist other suitable methods for transfer of materials like “no touch” processes, transferring sterilized items packaged with multiple sterile packaging layers or other technologies. Other technologies may arise. Proposed Change: delete: with accompanying disinfection of the exterior of the sealed packaging
1047-1051	Comment: Utilizing a risk based approach will focus monitoring of the appropriate items. Proposed change (if any): For materials, equipment, components and ancillary items that are necessary for aseptic processing but cannot be sterilized, an effective and validated disinfection and transfer process should be in place. These items once disinfected should be protected to prevent recontamination. These items, and others representing potential routes of contamination, should be included in the environmental monitoring program utilizing a risk based approach.
1072-1074	Comment: This statement on parametric release seems to be in an odd place. It is applicable to terminally sterilized products and is not specific to sterilization by heat. Proposed change (if any): Relocate to the general section on sterilization line 953, a more appropriate location in the document.
1115-1116	Comment: 8.57 Validation should include a consideration of equilibration time, exposure time, correlation of pressure and temperature and maximum temperature range during exposure for porous cycles and temperature, time and Fo for fluid cycles. These critical parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of sterilization validation and routine cycle acceptance criteria. Revalidation should be performed annually. Proposed change (if any): Add: In any case sterilization parameters during validation and in routine cycles must be in accordance with the registered marketing and manufacturing specifications
1147	Comment: See also 8.114 Proposed Change: …and validated to assure all product contact parts of the system are subjected…
1222	Comment: Ready to use (RTU) components like prefillable syringes or vials as well as Single use systems (SUS) often require ETO sterilization. Proposed Change: delete “method should only be used when no other method is practicable” or allow ETO sterilization explicitly for RTU components or SUS.
1258	Comment: the word primary implies there may always also a secondary sterilizing filter Proposed Change: delete “primary”
1258/1259	Comment: There is little rationale to recommend a second filtration for liquids and not for gases or venting. This to be addressed in the contamination control strategy applying QMR principles

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	Proposed Change: delete recommendation of a second sterilizing filtration
1285	Proposed Change: delete …"or better (e.g. 10 -7)".
1332-1333	Comment: Due to legacy equipment design and process considerations, it may not be possible to integrity test a filter in-line (or "on-line" as the annex states). Proposed Change: For new systems, it is recommended to perform the filter integrity test in-line with the filter, i.e., the filter is not removed from the system to perform the test.
1331–1334	Comment: In order to integrity test a filter, the test must be performed at atmospheric pressure. This may allow the integrity of the sterilized filter to be compromised and is in direct conflict with the last sentence of clause 8.63, where it states that once a system has been sterilized by SIP, it should remain integral prior to use. In addition, drains are prohibited in Grades A/B (clause 5.8), and as such, it may be impossible to integrity test the in-line sterilizing grade filter after it has been sterilized based on facility design and the process. Proposed Change: The pre-use integrity test is recommended; however, in cases where the integrity of the sterilized filter may be compromised by performing a filter integrity test post SIP of the filter due to design considerations, then the post-use filter-integrity test must be relied upon to verify the integrity of the filter.
1133 1134	Comment: The requirement is impossible to fulfill for equipment that must be wet prior sterilization as filter or UF membrane. In such case, the manufacturer must develop risk-based assessment to define an acceptable level of dryness for equipment wet using WFI prior to sterilization. Proposed change: Suggest to add at the end of the sentence 1134: "However, if the equipment has been wet using WFI (e.g. Ultrafiltration membrane) prior the sterilization process then a risk-based assessment should be carried to demonstrate the acceptable dryness level that will not impact the sterility of the equipment sterilized and the product sterility assurance level. The hold time between the wetting phase and the sterilization should be justified and validated."
1335–1336	Comment: It is not clear what is meant with "compliance is achieved" in the sentence "... this may not be possible; in these cases an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved." Compliance should be achieved with what? Proposed change : Please clarify: "...compliance is achieved." With what?
1259	Comment: the addition of a second sterilizing filter should be based on the product sterility assurance risk assessment result. As such, if the product or the aseptic process use could bring contamination or identify with a high level of residual risk then an additional filter should be placed. If a filter is stated as sterilizing filter then if the integrity is breach then this means the sterility of the product could not be ensured. If the manufacturer has filed in the AMM that two filters are sterilizing, then the situation is the same. Quid: What about existing process with one filter? Proposed change (if any): "the addition of a second filter through sterile, sterilizing grade filter (positioned as per clause 8.15), immediately before filling, should be added if the sterility assurance level identifies residual risk with

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	potential impact on the product sterility maintenance. The sterility assurance level risk assessment should include all the variables such as incoming control, raw material, equipment used, aseptic process, aseptic manipulation steps, aseptic intervention,...."
1331-1340	Comment: T~~here are t~~hree concerns (a, b, and c) were identified for this section: (a) The phrase "…in case of damage and loss of integrity caused by processing…" is recommended to be removed. If removing is not supported, it should be ~~or~~ revised as~~to~~ "…to determine if there was damage or loss of integrity prior to use…". (b) The word "immediately" is recommended to be removed as there could be a variety of interpretations on what immediately means. (c) It is recommended that a formal risk assessment~~based approach~~ be allowed for other situations than for small batch sizes. For example, filter applications where ~~the~~ high pressures are required to execute PUPS pose significant engineering challenges to single-use filtration assemblies such as burst tubing, broken vent filters, and leaks of process fluids in classified environments, despite good engineering design. Proposed change (if any): The integrity of the sterilized filter assembly should be verified by testing before use, in case of damage and loss of integrity caused by processing, and should be verified by on line testing ~~immediately~~ after use by an appropriate method such as a bubble point, ~~diffusive flow, water intrusion or pressure hold test. It is recognised that for small batch sizes~~ for some filtration processes, this may not be possible or may add additional risk.~~;~~ ~~i~~In these cases an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved. There should be written integrity test methods, including acceptance criteria, and failure investigation procedures and justified conditions under which the filter integrity test can be repeated. Results of the integrity tests (including failed and repeated tests) should be included in the batch record.
1349 - 1358	Comment: The process described for filter integrity testing and integrity assurance does not make sufficiently clear that filter integrity testing is not required BEFORE the process for the redundant filter. The part of the sentence "in case of damage during processing" should be removed for the following reason: Testing after the process is basically the only way to identify a damage during the process. 8.87 Where serial sterilisation filtration (one filtration is ~~immediately~~ followed by a subsequent – redundant? - filtration) is a process requirement, the filter train is considered to be a sterilizing unit and all sterilizing-grade filters within it should satisfactorily pass integrity testing both before use, ~~in case of damage during processing~~, and after use. 8.88 Where a redundant sterilisation filter is used, this ~~the additional~~ sterilised filter ~~sterilized~~ does not require ~~post~~ integrity testing, unless the primary sterilizing filter fails, in which case the redundant filter must then satisfactorily pass post-use integrity testing. (Note: if the product is known as "clogging", the way of integrity-testing should consider this circumstance; i.e. additional measures may be required to prove that filtration was effective throughout the process and successful filter integrity testing has not been caused by clogging. This may require involvement of a specialised laboratory.)

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1354	Comment: this is in contradiction with the point 8.78: the sentence demonstrates that the addition of a second sterilizing filter is not to improve the sterility. If a filter sterilizing integrity is breached, then the batch record in concerned is atypical to the other batch released. Meaning that potentially the sterility assurance level of the batch concerned by the failure is different or even lower than expected. As a matter of fact, if one sterilizing filter is not integer the batch status need to be investigated and maybe further testing or stability data would be needed. Generally, such situation leads to a QP discretion to release the batch depending on the AMM content. As a consequence, the proposed change is the following: Proposed change (if any): "Where a redundant sterilizing filter is used, the redundant filter does not require post-integrity testing unless the primary sterilizing filter fails, in which case the redundant filter must then satisfactorily pass post-use integrity testing. The batch should be considered as atypical, rationale and additional testing should be performed to ensure that the sterility assurance level of the product is safe for the patient."
Line 1356-1359	Comment: Location of sampling is still unclear. Proposed change (if any): Clarify that sampling should occur prior to the first filter of the filter train consisting of two filters in series.
1457-1458	Comment: A single control strategy, and an appropriate strategy term is needed which includes and distinguishes between the different approaches to controlling microorganisms, pyrogens and particulates which represent direct hazards to product quality and microorganisms, pyrogens and particulates which do not represent a hazard to product quality. Proposed change (if any): All control measures in place should be determined by the site's ~~contamination control strategy~~ microbial and particle control strategy.
1460-1461	Comment: Incorporate wording from ISO 13408 – 3, Aseptic processing of health care products (Part 3:Lyophilization). Proposed change (if any): The lyophilizer should be sterilized before each load or, under defined circumstances, before each campaign. The lyophilizer should be protected from contamination after sterilization.
1482	Comment: it is not clear that "unsealed containers" also refers to "partially stoppered / semi-stoppered containers" Proposed Change: Unsealed or partially-stoppered containers should be maintained under grade A environment.
1519-1522	Comment: The wording "designed to replace reuseable equipment" implies that SUS is only deployed in retrofitting situations. Proposed change (if any):

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	~~Single use systems (SUS) are those technologies~~ used in manufacture of sterile medicinal products ~~which are designed to replace~~ as an alternative to reusable equipment. SUS ~~are typically defined systems made up of~~ include individual components, and combinations of components such as bags, filters, tubing, connectors, storage bottles and sensors.
1530	Comment: If the use of SUS poses higher risk by the design of the assembly or increases complexity this use should be prohibitive. Turn it into a positive requirement: the use of SUS should reduce complexity of manual operations and the number of aseptic connections. Proposed Change: delete c) and d)
Line 540-545 and Line 1588-1590	Comment: Table 2 provides limits for settle plates in grade C/D area. However, it is not clear if this is necessary for grade C/D areas, which do not pose risk to the process. Proposed change: Add footnote that the use of settle plates in grade C/D area need to be assessed using a risk assessment considering the risk to process.
1594-1597	Comment: Relevant information for batch release are environmental control results from Grade A and B; Grade C and D environment has no direct impact on product quality.. Proposed change (if any): Suggest to precise for grade A/B environmental controls
1588 - 1597	Comment: the program for environmental and process monitoring program only list data trending while these data should be confirmed and back-up by periodic audit of the contamination control procedures and operation practices to establish the trend or deviation observed and be able to tackle the root cause of the issue. As a consequence, the sentence should be as followed: Proposed change (if any): “This program is typically comprised of the following elements: 1589 a) Environmental monitoring – non viable. 1590 b) Environmental monitoring – viable. 1591 1592 c) Aseptic process simulation (aseptically manufactured product only). d) periodic audit of the practices against contamination control procedures 1594 9.3 These key elements provide information with regards to the process and facility 1595 capabilities with respect to the maintenance of sterility assurance and the contamination practices/level.”
1615 - 1616	Comment: the pre-disinfection monitoring is not adapted because during the manufacturing and end manufacturing the monitoring is performed which encompass the pre-disinfection monitoring request in the draft. Also, the goal of the disinfection is to reduce, by a determined level, the microbial contamination which is confirmed based on the disinfectant qualification study and performance qualification of the disinfection procedure and periodic monitoring. Finally, the data generated may have no plus value for interpretation expect confirming the frequent isolated microorganism. This last data is generally analysed periodically

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	during the historical Environmental Monitoring data review. Proposed change (if any): Suggest to remove from the line 1615 “pre-disinfection”
1637-1639	Comment: During operations testing of inanimate surfaces should be avoided in order to minimize any unnecessary interventions into the critical area. In addition the removal of nutrient media on the surfaces would trigger additional interventions. Surfaces of critical areas should be monitored at the end of operations. (see also 9.27) Proposed change (if any): 9.11 Personnel should be monitored after critical operations. Results from monitoring should be considered when reviewing batch documentation for finished product release
1640	Comment: the Section does not contain the exceptions such as; is the monitoring requested if a specific area (with the same HVAC distribution system) is not used for a long period. The frequency of monitoring should be based on a risk-based assessment where the frequency of monitoring could be reduced. The same should apply for cleaning and disinfection of the cleanrooms not used for an extended period. Proposed change (if any): suggest to add: “when some area (with same HVAC section) are not used for an extended period of time. The frequency of cleaning and disinfection and/or monitoring could be reduced based on risk-based assessment and adequate procedure in place to avoid any contaminations.
1651	Monitoring should only be performed for 0.5 µm particles to be compliant with ISO14644-1 (ISO5)
1651-1652	Comment: Distinction should be made between ‘contamination’ - microorganisms, pyrogens and particulates which represent a direct hazard and risk to product quality and microorganisms, pyrogens and particulates which are not hazards to product quality. Proposed change (if any): Table 5: Recommended limits for airborne particle concentration for the monitoring of non-viable ~~contamination.~~particles
Line 1659-1662 Line 1703-1705	Comment: How often should the monitoring of 5 µm particles be taken? Continuous or periodic in the isolator and rRABS? Proposed changes: recommend to provide guidance on the monitoring frequency of 5 µm particles in the critical area. Should they be monitored at the same interval or continuously as for 0.5 µm particles. Also, provide guidance for all other areas (e.g. not critical) to be clear on expectation.
1651-1662	Comment: The significant figures are not consistent (5 µm vs 5.0 µm) in table 5 and Note 2. If this is not intentional, please use consistent significant figures throughout the document.
1659; 1703-1712	Comment: Further clarification is requested for the requirement of monitoring ≧ 5.0 µm particles during routine monitoring purposes, if it is not required for room qualification and classification purposes, given that macro particle counts especially ≧ 5.0 µm, may likely be false counts. A risk based approach could be

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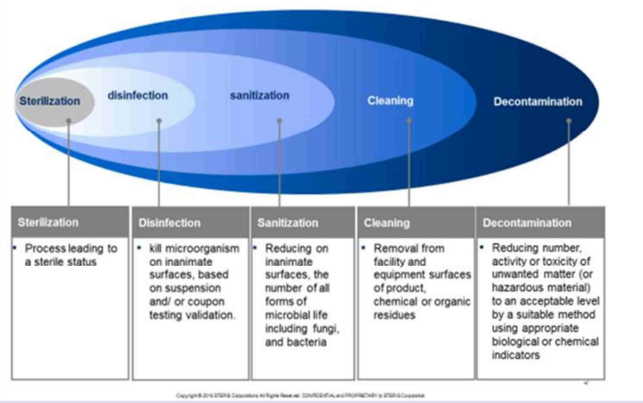
	utilized to determine the appropriate particle monitoring to be performed during qualification, classification and routine monitoring. Proposed change (if any):
Line 1683-1684 Line 1720-1722 Line 1747-1748 (Table 6)	Comment: There is a misconception that monitoring by settle plates is mandatory. Proposed changes: Recommend clarification that the type of monitoring methods used (active air or passive) should correspond to the operation being performed and risk assessment. While active air monitoring typically is the most sensitive and effective method, other monitoring such as settle plates may be justify when there is a disruption of unidirectional air flow of a critical operation.
Line 1720-1722	Comment: Surface sampling by swabs and contact plates is mentioned. Comment: As this section states that where aseptic operations are performed, a combination of methods such as settle plates should be used. Are settle plates also required in in supporting clean areas where critical operations are not performed, or that they are recommended as supporting data in addition to active air sampling, which is more likely to detect organisms that passive air sampling? Proposed change : Move 9.25 to line 1746, to clarify that the combination of tests should be justified in view of the nature of operations
1735-1736	Comment: Equivalence means that the upper level must be also be the same between the classical and RMM method. However the RMM method may also be superior to the classical method. This is typically the case for non growth based RMMs. Therefore RMMs should be demonstrated non inferior (=at least as good) to the classical method and not necessarily equivalent. Proposed change (if any): Rapid microbial monitoring methods may be adopted after validation as long as they are demonstrated to be non-inferior to the established methodology.
1741	Comment: monitoring outside operations is performed as continuous particle monitoring, continuous HEPA filtered air supply and cleanroom pressure differential. Proposed Change: delete 9.30
1744	Comment: Distinction should be made between 'contamination' - microorganisms, pyrogens and particulates which represent a direct hazard and risk to product quality and microorganisms, pyrogens and particulates which are not hazards to product quality. Proposed change (if any): Recommended action limits for ~~microbial contamination~~ microorganisms are shown in Table 6
1746	Comment: Distinction should be made between 'contamination' - microorganisms, pyrogens and particulates which represent a direct hazard and risk to product quality and microorganisms, pyrogens and particulates which are not hazards to product quality.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any): Table 6: Recommended maximum limits for ~~microbial contamination~~ microorganisms.
1753-1754	Comment: If 0 CFU is expected in Grade A the recommended limit should be defined with < 1 CFU Proposed change (if any): Change in Table 2 and 6 for Grade A
1774	Comment: The Section does not mention anything about APS for sterile APIs Proposed change (if any): Include some requirements for APS for sterile (small molecule) APIs
1817	Comment: performing inherent interventions during APS is required for personnel qualification. Often there are more inherent interventions required during APS than during a product fill. Proposed Change: delete …. at the maximum accepted frequency per number of filled units.
Line 1835 – 1836	Comment: Statement about bracketing or matrix approaches is not clear. Bracketing or matrix approach should be applicable not only for initial validation, but for the routine process simulation program as well. Also it is not clear by what is meant of the same container/closure configuration, as a bracket approach may encompass multiple container/closure configurations. Proposed change (if any): Reword to state “Bracketing or a matrix approach can be considered for initial validation as well as the subsequent routine process simulation program to encompass representative container/closure combinations”
Line 1850-1851	Comment: maximum permitted filling time needs clarification Proposed changes: consider including shift change for media fill duration
1882-1889	Comment: It is unclear if the requirement is 3 consecutive satisfactory simulation tests per each shift or 3 satisfactory simulation tests covering all shifts. If the requirement is per shift, then a 3 shift facility would require at least 9 process simulations for initial validation and 3 for the periodic revalidation. Consistent with PDA TR #22 Section 3.1, we recommend that it be revised to state the requirements per filling line or process. The impact of shifts can be designed into the process simulation program using a risk based approach. Proposed change (if any): Process simulation tests should be performed as initial validation, generally with three consecutive satisfactory simulations for each aseptic process and filling line ~~covering all shifts~~ ~~tests per shift,~~ and after any significant modification to the HVAC system, equipment, major facility shut down, process and number of shifts, etc. Normally process simulation tests (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process and filling line, and at least annually for each operator.
1921	Comment: identification of filled individual APS units which have undergone non-destructive weight checks is not possible in automated filling lines. Specific difficulties result of the use of isolator technology or fully robotic lines. Identification of these units requires implementation of specific track & trace technology like cameras and 2D matrix codes on each individual unit.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed Change: delete …identified and…
Line 1925-1926	Comment: No guidance is given how long can the media fill vials be sitting at room temp prior to incubation. Proposed changes: clarification that incubation of the media fill units need to be performed promptly at the established temperature (specified in the media fill SOP) after filling and visual inspection.
925-1930	Comment: ~~Comment:~~ We have 2 concerns; a) we recommend that direction consistent with PDA TR #22 Sections 4.5 and 4.8.2 be provided regarding APS requirements for products that are manufactured in opaque or primary containers that are not clear. B) we recommend that consistent with PDA TR #22 Section 7.6, examination can be performed by discharging incubated media into a clear container. Proposed change (if any): Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (i.e., amber glass, opaque plastic)- clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, at the conclusion of the test (after incubation), the media is discharged into clear containers for examination. Microorganisms isolated from contaminated units should be identified to at least the genus, and to the species level when practical, to assist in the determination of the likely source of the contaminant. The selection of the incubation duration and temperature should be justified and appropriate for the process being simulated and the selected growth medium.
1988 / 1989	Comment: The current wording in the draft Annex 1 is “Each sterilized load should be considered as different batches and require a separate sterility test.” Requirements for finished product testing should be based on Quality Risk Management principles. Requiring sterility tests for all sterilizer loads, regardless of type of sterilization process and/or controls in place, would lead to significantly more sterility testing for certain terminally sterilized products compared to aseptically processed products, which does not adequately reflect the sterility assurance risks associated with the different processes types. (The risk is significantly higher for aseptic manufacturing; however, no multiple sterility testing based on autoclave loads is possible and thus not required. With the new requirement, an additional burden is put onto the safer process. Sterilization processes have to be validated an regularly re-validated an carried out with qualified equipment. Process parameters are recorded and evaluated for each batch. It is acknowledged that each individual sterilized load should be represented in the batch sterility test, but the way of sampling and whether individual or combined sterility tests are performed should be based on further control measures implemented; thus again, the principles of QRM should be applied. This view is supported e.g. by ICH Q6 , section 2.6 Parametric Release “…These parameters can generally be more accurately controlled and measured, so that they are more reliable in predicting sterility assurance than is end-product sterility testing.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any): "Each sterilized load should be appropriately represented in the ~~considered as different batches and require a separate~~ sterility test."
1993/1994	Comment: Considering each sterilizer load a different batch leads to large increase of QC lab testing not only for sterility testing, but also for all other analytics; which does not appear meaningful as operations have to be performed with validated processes Proposed Change: delete Note in lines 1993/1994.
2018 - 2023	Comment: Terminology in the document is *alert limit* and *action limit* Proposed change (if any):
2076	Comment: "Clean non-classified" (CNC) is not the term commonly used Proposed change (if any): Controlled, not classified
2101	Comment: The definition of the word *component* does not comply with the use of the word in the text. Proposed change (if any):
2011-2015	Comment: Include a definition of open and closed RABS to align with ISPE definitions Proposed change (if any):
General – regarding the Glossary section:	**Comment:** Definition of the terms around cleaning, disinfection, decontamination, sanitisation and sterilisation should be defined to avoid confusion. Definitions should reflect ISO and EN documents (some indication is provided in *italics)*; however, the review team acknowledges that the finalization of the definitions requires some further consideration. The review team presents some suggestions for further consideration; among these, a diagram to present the scope may be useful; e.g.:  Note: The company providing this diagram may have a Copyright.

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*

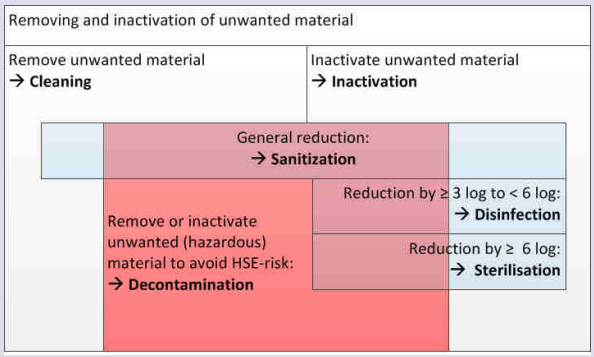
or:

In the following diagrams, colors indicate the following:

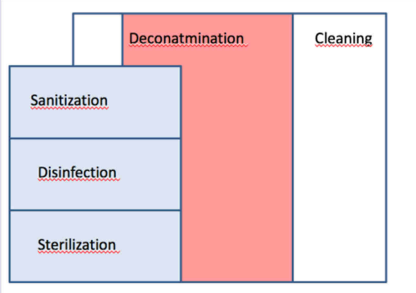
white: removing and / or inactivating any other kind of unwanted material; e.g. chemical substances, radioactive material, biological material (other than microorganisms)

blue: microbial reduction,

red: decontamination (removing or inactivating unwanted, hazardous material, i.e. for HSE reasons)



or:



1. Disinfection:
A process with the capability to kill microorganisms. The process should be validated based on suspension and / or coupon testing. *(see also USP 1072 and EN 14885)*

2. Disinfectant:

chemical agent that is able to reduce the number of viable microorganisms to a defined level *(ISO13408-&:2008)*

3. Sporicidal agent:

Agent that irreversibly destroys vegetative microorganisms and their spores under defined conditions

4. Sanitisation:

Line number(s) of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Operation to reduce undesirable microorganisms on inert contaminated surfaces depending on the objectives set (It is the action of reducing generally invisible contaminants from a surface) *(ISO2276:2007)* **5. Sanitising agent**: An agent for reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses, and bacteria. *(USP 1072)* **6. Decontamination:** reduce of unwanted, hazardous matter to a defined level *(ISO 9271:1992)* **7. Bio-decontamination:** reduction of biological contamination or its reduction to an acceptable level *(ISO 13408-6:2005)* **8. Rinsing program:** The rinse should be performed using water (the water grade depends on the area classification) to remove normal level of disinfectant or sporicide residue. However, if the level of residue is important (e.g., sticky, tacky, or slippery floors or doors) then a detergent should be used followed by a rinse using water. The rinse frequency should be set based on a visual inspection and tactile observations of the surfaces in the cleanroom. **9. Contamination** The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens), or of foreign particle matter, into starting materials (including the drug substance), packaging materials and / or drug products during production, sampling, storage or transport' with the potential to directly adversely impact product quality. **10. Contamination control strategy** *Include a definition of control strategy in the Glossary which is aligned to ICH Q10* A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.