Submission of comments on revision of:

‘Annex 1: Manufacture of Sterile Medicinal Products’

Comments from:

Name of organisation or individual
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1. General comments

General comment (if any)

1) From the general point of view, the revised Annex 1 is a comprehensive revision of the previous version. The main focus is on the application of Quality Risk Management in sterile manufacturing. The designation and description of the use of modern barrier technology, as the state of the art for aseptic manufacturing, has been well implemented. Some ambiguities and inaccuracies from the previous version have been rectified.

2) DIN ISO 14644-1, which is used by the European guide for the classification of cleanrooms, it appears the central document in the draft. The fact that the limit of 5 µm particles has been removed from the ISO 5 class sound positive. The change with regard to 5 µm particles in routine operation closes a regulatory gap, but still allows the manufacturers to continue measuring this particle fraction. Which is now consistent since an increased number of these particles indicates a problem.

3) Despite QRM principles application is strongly recommended, the presence a few mandatory requirements seems to be contradictory with this approach (ref. to detailed comments below)

4) The different requirements for terminally sterilized product vs. aseptic process are not presented with an adequate detail level. Together with the specific points on terminally sterilized products (8.1 to 8.5), any different expectation should be better explained in the different chapters

5) Requirements/expectations about raw materials (except water) are not covered in detail in the document, although raw materials are mentioned as one element of the contamination control strategy (line 79)

6) As far as sterile filtration, integrity testing after sterilisation and immediately before filling could have been left out, as the data from filter verification and the integrity testing after filling provide sufficient assurance.

7) In general terms, we observe that the use of the word "should" instead of "must" or “shall” may hinder the correct interpretation of a few requirements.

8) The use of the term “background environment” and “surrounding area” used in the document leads to confusion and misunderstanding. Some clarifications are needed.

9) There is general overlap with compendia requirements (e.g., on water systems and on visual inspection). This could lead to conflicting guidance in the future

10) The document contents should develop the requirements to support the manufacture of other products that are not intended to be sterile such as cell culture/fermentation. Currently, this is covered in ISPE and WHO and other guidance documents, but not in legislation.

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')*
26	Comment: Whole Section 2 – principle This section should include the principle that all products should be evaluated to determine if terminal sterilization is possible, before electing to use aseptic manufacture/processing. Proposed change (if any): To add text including that principle requires assessment of viability of terminal sterilization. Text should be similar to that in 8.30 of this document.
36	Comment: Appropriate "attitudes" requested for personnel is a requirement difficult to measure and assess Proposed change (if any): To remove the word "*attitudes*", keeping only "*skills*" and "*training*"
37	Comment: The personnel should have a specific focus on aseptic manipulation and protection of the sterile product. Proposed change (if any): To modify as follows: "*a specific focus on the principle of aseptic manipulation and in the protection....*"
45	Comment: Risk evaluation does not always allow scientific evaluations but in some occasion, it would be based on historical experience "by operators". Proposed change (if any): It is suggested to remove the term "*scientifically*."
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):" To replace with: "*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*."

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')*
104	Comment: It is not clear what it is considered to be "*more robust investigational tools*" Proposed change (if any): To clarify, suggesting possible additional tools
169	Comment: The potentially impacted batch could be located in a different line or in a different room, depending on the cause of non-conformity Proposed change (if any): To add.: "*even manufactured in other lines or in other rooms*"
196-208	Comment: The requirements for Grade A/B cleanrooms entrance seem to apply only to people performing manufacturing activities: requirements for access of people working without the product exposed (i.e. for cleaning, maintenance and/or validation activities) is not covered Proposed change (if any): To include guidance on requirement for people entering without the product exposed (i.e. gowning qualification and personnel monitoring. but not APS participation, as it is not in scope of their activity)
207	Comment: To clarify what continuous monitoring programs mean. Therefore, we suggest removing the term "continuous." Proposed change (if any): To replace with: *"…should also be an ongoing ~~continuous~~ monitoring program for personnel including some…"*
207	Comment: The use of continuous monitoring of gloves could introduce sources of potential contamination in the critical area. Proposed change (if any): It should be stated that the manufacturer could define, according to a quality risk assessment, which critical intervention needs microbial monitoring of personnel.
212	Comment: Disqualification could also be based on the a period of time passed from the last activity in A/B cleanrooms This period is to be determined, based on personnel experience and risk assessment. Proposed change (if any): To add: *", including the time not having entered in A/B cleanrooms*"
236	Comment: If the personal mobile phone is not allowed then this would mean that work mobile and computer should not be allowed. Therefore, we suggest considering those equipment entering in the same cleaning and disinfection process for items

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	entering within the cleanrooms. Proposed change (if any): To add the following sentence "*if a work-related device (computer, mobile, etc…) should be entered in the cleanroom, appropriate cleaning and decontamination should be applied*"
254	Comment: The disinfection means that the process of disinfecting has been qualified and validated based on the surface that needs to be disinfected. Therefore, the word disinfection is not appropriate. Proposed change (if any): To modify the sentence as follow: "*A general protective suit and appropriately cleaned and sanitized shoes or overshoes should be worn"*
274	Comment: Some production activities may require precise manipulation and therefore the wearing of the eye covering or gogle may have a negative impact on the product and the microbial contaminations control. Proposed change (if any): To add the sentence "*eye covering is not required when the use thereof impair the ability of the personnel to conduct the assigned task (e.g. pipette sampling)*"
277	Comment: Facility socks are required to be worn before grade C and B: however, socks change before entering may increase contamination risk Proposed change (if any): To specify if socks can be worn in the general changing area and not immediately before entering grade C and B gowning rooms
282	Comment: The wording "working session" is not clear. Does it mean that a working session is considered as a working shift? Therefore, we suggest adding the definition of a "working session" Proposed change (if any): "*Working session = enter in a grade A/B and leave the grade A/B*"
283	Comment: The use of regularly disinfected gloves during operations does not allow personnel to touch surfaces where the product is exposed. Proposed change (if any): To specify that, although sanitized gloves are used, surfaces where the product is exposed should be touched only with appropriated sterile or sanitized tools

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288-291	Comment: Further details on the way how to treat garments (for instance handling them on classified areas or using HEPA/ULPA filtered air for drying) may be given. Inspection for integrity is a critical activity that should be done by trained personnel according to adequate procedures and by training. Proposed change (if any): To specify about the treatment of garments and the trained personnel for inspection of their integrity
322	Comment: Why to hold specific limits for air velocity, if the height of measurement must be justified. Why not focusing on unidirectional flow and avoidance of contamination? The air velocity should be based on the smoke study, criticality of the operations and the design of the equipment. Proposed change (if any): "*Unidirectional air flow systems should provide a homogeneous airspeed demonstrated based on the smoke study linked to the criticality of the operations, air velocity and the design of the equipment risk analysis results*"
325	Comment: Measuring air speed "*close to the terminal air filter face*" does not guarantee that the speed at the working surface will be adequate. Proposed change (if any): It's better leaving only the second option "at working height", agreeing that it may be at 1-1.5 m above the working surface.
335	Comment: It is stated that "*only grade C cleanrooms should interface with the grade B aseptic processing area*". This could be interpreted as: 1) rooms with a direct air passage to Grade B, where material or personnel may enter Grade B (e.g. via a door) shall be Grade C, <u>or</u> 2) rooms from which Grade B is accessed in any way (including, for example, via an actively ventilated pass-through) shall be Grade C). If interpretation 2) is correct, it may result in significant physical and/or operational modifications for some facilities. Not only where Grade B and Grade D may interface via an additive pass-through, but also where Grade A or B areas interface with Grade D or lower classified areas in an "exit only" manner (e.g. where a high pressure differential through a wall opening and a conveyor system allows the transfer of fully integral containers for inspection and/or labelling operations). Proposed change (if any): It is suggested to better clarify this statement
336	Comment: It is to be noted that it is frequent to have a direct exit of closed containers to the CNC packaging area from A/B areas

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	Proposed change (if any): It is suggested to consider this situation
354	Comment: Sealing of false ceilings is especially critical in areas with negative pressure, and it may be mentioned here. Proposed change (if any): It is suggested to mention this critical situation
365	Comment: The sentence leads to misunderstanding: if the testing must be done during qualification or routine monitoring? And is the requirement applicable for entrance/in or exit/out airlock? Proposed change (if any): "*for entrance airlock, the final stage of the airlock should be the same grade as the area into which it leads when tested at-rest state*."
379-381	Comment: The requirement for airlock leading to grade A and B is inadequate because it is not feasible to have a qualification list of equipment/material allowed to be transferred in. This means that the airlock would be treated like a sterilization load qualification. Finally, this is only applicable for VHP airlock. Proposed change (if any): " *All materials/equipment entering in grade A and B area should be subject to a validated disinfection procedure*".
382	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*."
385	Comment: Items inside A/B areas should be kept at their minimum number, leaving out of the area anything which is not frequently used Proposed change (if any): It is suggested to add this recommendation
390	Comment:

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	The movement of material should be based on QRM for all stage and all classification area. As a matter of fact, the contamination control strategy must encompass the facility, as a consequence, be developed using QRM principle. Therefore, the movement of material from CNC to grade A should be based on QRM principle. Proposed change (if any): To replace the sentence 390 by "*The movement of material from clean not classified to grade A should be based on QRM principle....*"
394	Comment: A system is usually in place to allow operators leaving the rooms in case of emergency. Proposed change (if any): It is suggested to mention this situation
400	Comment: The requirement is only applicable for grade C to grade A. Proposed change (if any): "*for grade A, B and C, HEPA or ULPA filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively*"
412-421	Comment: Smoke tests are required in Grade A/B to assess unidirectional flow: however unidirectional airflow is typically not required in Grade B areas. Proposed change (if any): It is suggested to specify the requirement of smoke test only when unidirectional airflow is required (Grade A)
440	Comment: Assessed and control is not sufficient. Any activities that potentially compromise the sterility assurance of critical zone or not should be assessed. The risk identified must be removed or mitigated to reduce the risk level. Proposed changed (if any): "*Any activities that potentially compromise the sterility assurance of critical zone or not should be assessed and mitigate to reduce the risk level by modifying or adapting the process in place. The risk could not be removed then appropriate control should be applied.*"
457	Comment: Typo error: remove 'and'
460	Comment: The term "decontamination" used is not suitable, 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 fact, a sporicidal agent does not generally contain surfactants in their formulation, therefore, no cleaning action is possible. Only mechanical operations could be achieved

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	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, ...*"
460-470	Comment: This new clause specifies limitations (albeit broad) under which the Grade D "minimum" is permissible. The inference is that some isolator installations do not meet the requirements to be sited in the minimum (Grade D) background (e.g. closed systems without sporicidal decontamination, or any installation with unusually high risks for contamination). This could be a significant non-compliance risk for some older isolator installations and require update to decontamination regimes, or even background environments Proposed change (if any):
472-478	Comment: Physical gloves leak test performed during production is laborious and may compromise the whole Isolator aseptic conditions. even in case of single leaking glove Proposed change (if any): It is suggested to specify that, during production, a detailed visual check can be adequate, requiring physical check only at the beginning and at the end of batch/campaign. Also to specify the difference between physical and mechanical test.
474	Comment: The materials used shall be demonstrated to have good mechanical and chemical resistance according to the product or process performed. Proposed change (if any): It is suggested to add this recommendation
534	Comment: Clean up period to pass from "in operation" to "at rest" is not given. 15-20 minutes, as stated in the previous version, was a guidance value very useful. Proposed change (if any): It is suggested to mention the time of 15-20 minutes, as an indication
540	Comment: The document does not specify the need of "*at rest*" microbial qualification to define the environmental microbial baseline. Proposed change (if any): To specify to perform a periodic "*at rest*" microbial qualification, whose frequency should be risk based assessed.
544	Comment:

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	The specification for grade A based on the note of the table 2, is 0 CFU. Therefore, we suggest to put in the table 2: 0 CFU for grade A.
549	Comment: It is to be considered that if the plates are left for more than 4 hours, their fertility during the period they are left should have been validated Proposed change (if any): It is suggested to consider this situation and to add this recommendation
558-561	Comment: The document is based on a QRM principles and sponsors the use of a QRM approach to justify the program put in place in a sterile manufacturing. Therefore, imposing a frequency of requalification is not in line with the QRM principle promoted in this document and the recent review of the EU GMP documents. Also, it is not in line with the requirement of the ISO 14644 part 2. Proposed change (if any): Delete the second sentence; 559 to 561.
567	Comment: The section “disinfection” should be replaced by “*cleaning and disinfection*”
570	Comment: A separate cleaning should not be mandatory prior each disinfection. Current disinfectants on the market are formulated with surfactant that has the capability to clean and disinfect in a one step. However, it should be state that if the surface to be cleaned and disinfected contain high level of soils then a cleaning step prior disinfecting may be needed. Proposed change (if any): Remove the sentence between brackets.
571	Comment: Disinfectant use is unlikely to lead to microbial resistance development. Therefore, the obligation for disinfectant rotation is not scientifically supported and should limited based on historical EM data review to add another disinfectant if the microbial data suggest it. Proposed change (if any): “*the rotation of disinfectant along with a sporicidal agent should be based on a QRM approach and the results of the periodic review of the historical EM data trending*”
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".

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	Proposed change (if any): "effectiveness of the disinfection program and to detect the presence of resistant and/or spore forming strains"
577	Comment: The "cleaning program" term is not appropriate because the goal is to remove residue of disinfectant or detergent. Therefore, we suggest using the term "rinsing program". Proposed change (if any): " *rinsing program should be effective in the removal of disinfectant and detergent (if used) residues*."
580	Comment: It is proposed to remove the "*should be monitored for microbial contamination*", as the dilution and the storage would be validated. Proposed changed (if any): "*Disinfectants and detergents; dilutions should be kept in previously cleaned containers….* "
588	Comment: While VHP is currently the most widely used method of vapour disinfection, it is hard to understand why it has been singled out, when several other methods have been shown to be comparably effective (e.g. NO2, Cl2, O3 and ionized hydrogen peroxide, which is distinct from VHP). The singling out of VHP is unnecessary and risks creating industry bias toward that technology. In time, it may also appear outdated if other technologies surpass VHP. Proposed change (if any):
597	Comment: 6.2 Equipment monitoring requirements should be determined during qualification. Process alarm events should be reviewed and approved and evaluated for trends. Not enough control described. Proposed change (if any): Language similar to that used in 6.3.5 ISO 11135 required. **6.3.5** Means shall be provided to ensure that failure in a control function does not lead to failure in recording of process variables such that an ineffective process appears effective. NOTE: This may be achieved either by the use of independent systems for control and monitoring or by a cross-check between control and monitoring which identifies any discrepancies or indicates a fault.
611	Comment: This clause highlights an apparent disconnect between the specifics of its intent (product contact equipment requiring disinfection and/or sterilization) and the subject matter of the section ("Equipment"). Additional context is required in this section so that the reader can understand clearly which clauses apply to given equipment types (e.g. product contact vs non-product contact). Notwithstanding the lack of context, the new cleaning validation clause adds little, that is not currently understood as a requirement for sterile processes Proposed change (if any):

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621	Comment: Typing error: “qualificion” Proposed change (if any): Correct (qualification)
629	Comment: ISO 14644 provide instructions on particle counter qualification Proposed change (if any): It is suggested to add reference to ISO 14644
631	Comment: If it is a requirement to use isokinetic sample heads, guidance should be given on their positioning height Proposed change (if any): To add the sentence “*the isokinetic sample heads should be as close as possible to operations*”
637	Comment: Chapter 7 (Utilities) appears to be a chapter about WFI, with some small acknowledgement of other utilities. Expectations around some critical utilities (e.g. pure steam or sterile compressed gas) are arguably insufficient, however, further expansion might lead the chapter into design guidance territory. Alternative approaches (for example, as “utilities” and “process water systems” sub-sections under the Equipment chapter) should be considered. Several clauses in chapter 7 use the term “water system” (some refer specifically to Water For Injections (WFI), but no other grades are mentioned). While the intent appears to be that the term “water system” refers to treatment of water for the distribution to and use directly in the process, the lack of definition could lead to confusion. For example, should a pre-treatment/feed-water plant be considered a “water system”? Proposed change (if any):
667	Comment: The document does not define formally “water systems”. Proposed change (if any): To define in the Glossary “Water Systems embrace Water treatment plants and distribution systems”.
683	Comment: Monitoring and maintenance of filters are not clearly described. It is not clear if the point refers to filters installed in water production steps, or in the recirculating loop, or at the point of use. Proposed change (if any): To clarify where filters are allowed/recommended and what kind of maintenance and monitoring is required for them.
689	Comment:

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	Integrity tests of vent filters involve risks operations in the system. Therefore, the integrity testing frequency should be established according to a risk assessment, taking into account that the water system is also qualified and routinely monitored. Proposed change (if any): To change the sentence as appropriate and, instead of saying that integrity should be tested "*before and after use*" it should say "*before and after sterilization process*", as it is used in continuous
691-695	Comment: Effective cleaning and sanitization or cleaning and disinfection or cleaning and sterilization process must be performed to remove the 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. To clarify the term used "regeneration" Proposed change (if any): "*7.13 To prevent the formation of biofilms, cleaning or sanitization or disinfection or sterilization of water systems should be carried out according to a predetermined schedule, as determined according to the investigation findings and by QRM principles. Sanitization or disinfection step of a water system with chemicals should be followed by a validated rinsing procedure. Water should be analyzed after the cleaning and sanitization or cleaning and disinfection…"*
695	Comment: For microbiological analysis, most organisations would re-commence system use at-risk, while waiting for results which may take several days. Allowance for this appears to be an oversight in the draft. If this action is no longer permissible, this requirement has significant impact Proposed change (if any):
701	Comment: Sampling from the worst case location each time water is used is unclear and seems too restrictive (since water is used several times in a day). Additionally, the example of the return point as worst case location can be interpreted as mandatory. Generally this expectation seems to be a "quality by testing" requirement Proposed change (if any): To better specify the requirement (i.e. each day of manufacturing) and to remove the example, as return may always not be the worst case. Consider removing sampling frequency requirements similarly as Environmental Monitoring
702	Comment: The alert limit should be periodically reviewed/assessed based on the historical data/trends. Proposed change (if any): " *performed with alert limits based on the qualification and historical data that will identify an adverse trend in"*
705	Comment:

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	The requirement is not applicable. If this statement were taken literally, some manufacturers would be required to take hundreds of samples each day. Tracking the need for a sample would be nearly impossible and it would likely take multiple additional staff to meet the requirement. Suggest removing "each time" It is much more likely that the clause is supposed to read "… *each day the water is used* … " or include another alternative word to "time" which keeps sampling requirements to a more sensible number. Proposed change if any: "distribution loop return, should be included in the monitoring program the water is used for manufacturing"
710-711	Comment: TOC and conductivity Proposed change (if any): TOC and/or conductivity
713	Comment: This header could be misinterpreted. For moist heat sterilization steam is the sterilizing agent and should be a higher quality than steam used in ethylene oxide sterilization for preconditioning / conditioning. Proposed change (if any): Change header from '*Steam used for Sterilization'* to '*Steam used as sterilizing agent'* Note: is definition of 'sterilization agent' is needed, refer to definition in ISO11139
715	Comment: Requirement of "low" level of endotoxin for steam generator feeding PW is too vague: additionally it is not clear whether this should be a routine testing Proposed change (if any): To specify requirement and if a routine endotoxin testing is required for PW feeding steam generators
777	Comment: This operation, in a few cases, could not be possible due to product characteristics Proposed change (if any): To add "*when it is possible*"
792	Comment: To add *aseptic process* in the glossary
815	Comment: Unloading of a lyophilizer is to be removed, as it can be performed in grade A air which is not the same as a grade A
848-850	Comment:

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	The final sterile filtration should be carried out as close as possible to the filling point and downstream of aseptic connections wherever possible. It seems that this statement suggests that, within the overall steps of the manufacturing operation, the sterile filtration step should be performed as close as possible to the filling step. By not having additional steps in between these two steps, the potential for contamination is minimized. This same general point is also made with lines 1258-1261 which state "*Due to the potential additional risks of a sterilizing filtration process as compared to other sterilization processes, a second filtration through a sterile, sterilising grade filter (positioned as per clause 8.15), immediately prior to filling, is advisable."* The text in lines 848-850 also states that the final sterile filtration should downstream of aseptic connections wherever possible. This same point is also stated in lines 1272-1279 which states that "*The filtration system should be designed to:… Minimise the number of aseptic connections required between the sterilizing filter and the final filling of the product.*" The meaning of the word "close" within the sentence "*the final sterile filtration should be carried out as close as possible to the filling point*" in lines 848-850 is not referring to physical closeness in terms of distance (e.g. 9 feet is better than 12 feet), it seems that the intent of this statement is that one should minimize the potential of contamination between the filtration step and the filling step. Proposed change (if any): Since the intent of points of lines 848-850 is covered elsewhere, it is suggested to delete these lines completely to avoid the confusion.
866	Comment: The requirement in the *point d)* need to be removed, as it is validated in the aseptic hold time.
892	Comment: The frequency of testing should be defined. Should all batches be tested? Only during initial process validation? Only in on-going stability batches? Proposed change (if any): It is suggested to mention that the testing conditions and time are to be determined based on the application of QRM principles
899	Comment: Since the laminarity of the flow can be compromised by an air extraction system, the need for an extraction system should be considered based on a risk assessment. Proposed change (if any): It is suggested to mention this situation.
931 - 932	Comment: If critical defects are identified during subsequent sampling, this doesn't mean failure of the original inspection process since the latter is probilistic in nature. Some companies have categorised particulate matter as a critical defect and after any inspection process such defects can still be present in a batch.

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	Proposed change (if any): Adopt AQL limits as indicated in USP <1790>, allowing for the process to pass when minute quantities of critical defects are detected.
953-1248	Comment: In the chapter about sterilization, no mention is made to other methods, such as peracetic acid, VHP or white pulse light. Proposed change (if any):
955	Comment: If a terminal heat treatment to reduce bioburden (e. g. pasteurization) is used for aseptically manufactured products, is the parametric release allowed? Proposed change (if any): To define parametric release strategy for such a kind of manufacturing.
966	Comment: Requirement of a formal investigation for sterilization failure seems to be too restrictive and not value-added especially when the root cause is immediately evident Proposed change (if any): It is suggested to add: "*Investigation need and formality level should be evaluate case by case by QRM principles*"
982	Comment: What is expected as verification? This is a vague statement. Proposed change (if any): Refer to ISO 11135 D.12.3.3
996	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 supplier history and testing data, the supplier audit and the sterility risk assessment results.*"
997	Comment: Contradictory requirements between 8.38 and Glossary about the need of D-value verification as incoming test for BI

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): It is suggested to add: "*The need of check D-value of incoming BIs should be assessed by QRM (i.e., for qualified Suppliers, the Supplier CoA verification may be adequate)"*
1078	Comment: The requirement that "*Monitoring and recording systems should be independent of the controlling system*" does not clarify whether the instrument could be the same with two signals, one for control and the other for monitoring, or not. A unique system with independent sensors is to be considered adequate. It is standard practice today having a SCADA, controlling and monitoring (through a display) the cycles, while recording is the process done independently. The way it is written seems not to allow such a current practice. Proposed change (if any):
1100	Comment: Requirement of investigation for each non-compliant item from sterilization loads seems to be too restrictive and not value-added, especially when the root cause is immediately evident Proposed change (if any): It is suggested to add: "*Investigation need and formality level should be evaluate case by case by QRM principles*"
1133-1134	Comment: The requirement is impossible to fulfill for equipment that must be wet prior sterilization as filter or UF membrane. In such a case, the manufacturer must develop a risk-based assessment to define an acceptable level of dryness for equipment wet using WFI prior to sterilization. Proposed change (if any): It is suggested 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 holding time between the wetting phase and the sterilization should be justified and validated.*"
1148	Comment: The pressure and time do not depend on the location. Pressure and time should be monitored with one sensor and temperature with several sensors in critical locations. Proposed change (if any):
1152	Comment: It is a good practice to over-pressure the system after SIP whenever possible. Proposed change (if any): It is suggested to add this operation
1195	Comment: Chamber pressure is not a critical parameter, in this case, for the sterilization process. If the intention is to prevent air

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	entering the chamber from the outside areas, it should be mentioned, as it has the same relevance as in any other room where overpressure is needed. Proposed change (if any):
1217	Comment: Density of product should also be considered Proposed change (if any): To replace the sentence at point 8.71 with: "*Validation procedures should ensure that the effects of variations in density of the product and packages are considered*".
1222	Comment: The statement "*when no other method is practicable*" is vague. What should be done to demonstrate that no other method is practicable?
1225	Comment: The statement "*and reaction products to defined acceptable limits*" is vague. What are the formal requirements for ethylene oxide residuals in drug products? IS EMA_CVMP_271_01 Guidance on the use of EO in the manufacture of medicinal products" still valid or do we have to apply ICH Q7? Or other? Proposed change (if any): Reference or give guidance to set limit.
1230	Comment: The text requires clarification Proposed change (if any): It is suggested to replace the sentence with: *"The nature and quantity of packaging materials can significantly affect the efficacy of the process*"
1236	Comment: In order to minimise operator, contact with sterilized products, it is common practice in Ethylene Oxide sterilization to use process challenge devices (PCD) which are placed on the external surface of the sterilization load. These PCD's contain a Biological Indicator and are typically shown to be more challenging to the sterilization process than the natural bioburden on the product and the product test units containing Biological Indicators which were placed within the load in validation. Therefore, text should be modified to permit this approach Proposed change (if any): To replace the sentence at point 8.75 with: *Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load at defined locations, shown to be 'worst-case' during validation, unless parametric release has been authorized by the National Competent Authority.*

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1258 -1261	Comment: The word “second” adds confusion to this sentence. Companies/inspectors could interpret the word “second” to mean that it is advised that there be two sterilizing filters in series with both of them being located immediately prior to filling (the concept of having a redundant filter) which is not the intent of this statement. Proposed change (if any): It is suggested to modify the sentence as follows: *“Due to the potential additional risks of a sterilizing filtration process as compared to other sterilization processes, a ~~second~~ filtration through a sterile, sterilising grade filter (positioned as per clause 8.15), immediately prior to filling, is advisable.*
1287	Comment: Integrity testing of filters prior to filtration does not add assurance in terms of product quality. If compliance is to be managed in a risk-based way, this requirement should be reconsidered. The likelihood of detecting a failing filter that would not be detectable after use is very small compared to the likelihood of contaminating the process with the testing solution. The associated costs are not proportional to the risk being avoided. Proposed change (if any): It is suggested to do testing prior to filtration, based on QRM, e.g. if there is any possibility that the filtered medium would clog an opening in the filter membrane.
1331-1334	Comment: The text states that “after use integrity testing” should be performed “on line”. The term “on line” is not clear and it could be interpreted differently by different companies/inspectors. Examples of different interpretations: “On line” interpretation #1 = the filter assembly must remain installed, as it was during the filtration operation and the integrity testing must be performed with the filter installed in the filtration train. “On line” interpretation #2 = the filter element must remain in the same filter housing during the post use integrity test (this could be applicable when a filter element is installed in a stainless housing). From a sterility/patient safety perspective, interpretation #2 is important. It is not a good practice to remove the filter element from the housing and then perform the post use testing of the filter element with it installed in another housing because this could potentially mask an installation/sterility problem during the filtration operation. The post use integrity test should be performed with the filter still installed in the filter housing that it was installed in during the filtration operation, but it is acceptable to remove the filter assembly (filter and housing as a unit) to perform this testing at a location other than in the filtration train. Interpretation #1 adds an additional restriction for the manufacturing operation (ties up the filtration line during the time required to perform the post use integrity test) but it does not reduce any sterility/patient safety risk because it is not feasible that an improperly installed filter element would become properly installed during transport to the off line integrity test station. If the proposed change is made, the focus of the statement will be on interpretation #1.

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	Proposed change (if any): To replace the sentence as follows: *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 <u>while installed in the same housing</u> by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test.*
1334	Comment: What is a “small batch” size? Proposed change (if any): To specify small batch size
1349	Comment: Difference between serial and redundant filtration is unclear Proposed change (if any): To specify in the Glossary the two cases
1360	Comment: The requirement of filter discard after a single lot seems too restrictive as it will not allow mono-product campaign Proposed change (if any): To better specify this requirement considering QRM principles and the potential impact for industry
1372	Comment: It is not clear if BFS containers are considered FFS units, to be sealed by fusion and therefore to be 100% integrity tested. Proposed change (if any):
1387	Comment: If a “pre-mould” container is produced in-line by a separate machine, is that still considered to be a ‘one continuous operation’?
1460	Comment: Sterilizing of lyophilizer before each load may not be required, based on current loading technology that can maintain aseptic conditions over several batches. Proposed change (if any): It is suggested to specify that the sterilization frequency of the lyophilizer should be determined based on the application of QRM principles
1588-1595	Comment: The data trending should be confirmed and supported by periodic self-inspection of the contamination control procedures

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	and operation practices, to establish the trend or deviations observed and to be able to tackle the root causes of any issue. Proposed change (if any): To replace with the following sentence: *9.2 "This program is typically comprised of the following elements:* *a) Environmental monitoring – non viable.* *b) Environmental monitoring – viable.* *c) Aseptic process simulation (aseptically manufactured product only).* *d) Periodic audit of the practices against contamination control procedures* *9.3 These key elements provide information with regards to the process and facility capabilities with respect to the maintenance of sterility assurance and the contamination practices/level."*
1615-1616	Comment: The pre-disinfection monitoring is not appropriate because, during the manufacturing, monitoring is performed according to the pre-disinfection monitoring procedure, as request in the draft. Furthermore, the goal of 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 additional value for confirming the frequency of isolated microorganisms. This is generally analysed periodically during the historical Environmental Monitoring data review. Proposed change (if any): It is suggest to remove from the line 1615 "*pre-disinfection*"
1629	Comment: "c" not in capital (typing error) Proposed change (if any): "Grade B, C and D"
1640	Comment: The Section **Environmental Monitoring** does not include the request of monitoring when a specific area (with the same HVAC distribution system) is not used for a long period of time. 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): It is suggested 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*".
1661	Comment: If 5.0 micron particles are not measured during qualification, it will no longer be possible to set alert limits based on qualification data.

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	Proposed change (if any): To remove '*and qualification data'*
1707-1712	Comment: It should be specified that it is applicable to grade A in "operation", as for grades B, C, or D, it is not rare to have counts of particules ≥ 5.0 µm. Proposed change (if any):
1721	Comment: It would be useful to provide guidance about air grade and for sampling frequency when cleanrooms are not in use
1728	Comment: The requirement of "*continuous monitoring*" for viable in grade A/B should be clarified, as current methods have serious limitations (especially active air sampling) Proposed change (if any): To clarify if settle plates continuously exposed can fulfil the requirement or if different expectations are linked to this statement
1735	Comment: The application of rapid microbiological test should not completely replace the established methodology. Proposed change (if any):
1744	Comment: Recommended limits are expressed in CFU, while current available technologies may express contamination values differently and with an increased sensitivity Proposed change (if any): To clarify that, with more sensitive methods, different limits may be applied, if scientifically defendable and linked to the alternative method sensitivity
1744	Comment: Limits for operators' gowning routine monitoring are not specified Proposed change (if any): To specify these limits clarifying whether surface monitoring limits can be applied
1768	Comment: Evaluation on product quality impact of each isolated microorganism from Grade B zone is not scientifically justified, since these organisms are not expected to get in contact with the product Proposed change (if any): It is suggested to limit this expectation to Grade A isolated microorganisms, considering that more stringent requirements may be applied in specific cases, according to QRM principles

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1768	Comment: Requirement of ID for all Grade B isolated microorganisms is not in line with QRM principles Proposed change (if any): ID requirements should be based on QRM and be specific for a given facility/environment
1777	Comment: When writing “and/or” it means that only placebo can be used in Media Fill testing, when it is clear that it should be always a nutrient media with or without placebo. Proposed change (if any): It is suggested to clarify this sentence
1806	Comment: Lyophilization cycle duration is included within the process parameters that should be fully simulated during Media Fills, while it may be not significant to assess the sterility assurance of the aseptic process Proposed change (if any): To better clarify if a shorter cycle can be applied for Media Fill, if supported by the application of QRM principles
1813	Comment: Difference between *inherent* and *corrective* interventions is not clear Proposed change (if any): To clarify difference between inherent and corrective interventions and to specify if the related requirements are applicable also to Isolators (i.e. same number of interventions between routine manufacturing and APS)
1882	Comment: The requirement of performing a Media fill prior to shut down or inactivity period seems to be unnecessary, as this is more a business risk consideration Proposed change (if any): It is suggested to remove this requirement or to clarify the detailed situations when this is expected
1883	Comment: Requirement of 3 consecutive media fill “per shift”: this statement is not clear. Usually, requirement is having 3 successful runs per line and not per shift. Every shift could be involved in a media fill as a basic qualification requirement. Proposed change (if any): To better clarify this statement
1911	Comment: Requirements in case of contaminated unit(s) in APS are unclear and contradictory: 3 repetitions seem to be always

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	recommended Proposed change (if any): To specify that, when root cause has been identified and removed, a single repetition can be adequate if supported by a robust investigation and by QRM principles
1920	Comment: "*Other units*" repeated twice (statement unclear) Proposed change (if any): This statement is unclear: clarify whether it is a typing error
1925	Comment: It is mentioned "*filled APS units should be incubated in a clear container*". It is not clear if the filling should be done in clear containers or if, after filling, the container is not clear, the media should be transferred into a clear container that is the one to be incubated. In fact, in some cases the APS units are not clear, as the case of ointments filled into aluminium tubes. Proposed change (if any): To better specify this point
1928	Comment: It is requested that "*the selection of the incubation duration and temperature should be justified*". It would be easier to make reference to the sterility test pharmacopoeia requirement or to state that it should be done for 14 days and at the requested temperature conditions. Proposed change (if any):
1941	Comment: This is a different approach than the one given in 9.43. In 9.43, lines 1916-1918: "Typically 3 successful consecutive repeat APS would be expected; any differences to this expectation should be clearly justified prior to repeat performance" In 9.47, lines 1941-1942: "The number of repeat successful APS prior to resuming production should also be justified." Proposed change (if any): It is requested to clarify if 3 successful consecutive repeat APS are acceptable or further justification is to be produced.
1958	Comment: A suggested limit for bioburden would be of great help to avoid discussions Proposed change (if any):
1983	Comment: Please clarify the meaning of *significant intervention*

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2007	Comment: The application of rapid microbiological test should not completely replace the established methodology. Proposed change (if any):
2145	Comment: Grade A air supply definition is unclear and not detailed about the monitoring location height Proposed change (if any): To clarify in details the engineering, quality and monitoring expectations for a “grade A air supply”
2163	Comment: Isolator Requiring isolators to comply with grade A zone, especially in closed systems, is not appropriate, as the isolator is closer to a sterilizer than to a room. Therefore, if contamination is absent (because the closed environment has been sterilized with a validated cycle), the requirement of complying with grade A is not justified as well as it is not requested for an autoclave. Proposed change (if any):
2011	***11 Glossary*** Definition of the following words should be described and improved, as followed. Definition-use should be in line with ISO and EN documents: 1. *Disinfection*: a validated process which demonstrates a reduction of the number of microorganisms in or an inanimate matric, achieved by the irreversible action of a product on their structure or metabolism, to a level judged to be appropriate for a defined purpose. 2. *Disinfectant*: a chemical agent that can reduce the number of viable microorganisms (ISO13408-&:2008) 3. *Sporicidal agent*: An agent that destroys bacterial and fungal spores when used in sufficient concentration for specified contact time. It is expected to kill all vegetative microorganisms. (USP1072) 4. *Sanitization*: The operation, used to reduce undesirable micro-organisms on inert contaminated surfaces depending on the objectives set (It is the action of reducing generally invisible contaminants from a surface) (ISO2276:2007) 5. *Sanitizing 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*:

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	Reducing number, activity or toxicity of unwanted matter (or hazardous material) to an acceptable level by a suitable method using appropriate biological or chemical indicators 7. ***Bio-decontamination***: removal of microbiological 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 or observations of the surfaces in the cleanroom.