20 March 2018

European Medicines Agency
30 Churchill Place
Canary Wharf
London E14 5EU
United Kingdom

via email to SANTE-REVISION-OF-ANNEX-1@ec.europa.eu

Dear Sir or Madam:

The International Society for Pharmaceutical Engineering (ISPE) would like to submit comments on the revision of Annex 1, on manufacturing of sterile medicinal products, of the Eudralex Volume 4.

These comments were developed by an international team of ISPE subject matter experts and represent the input of ISPE technical communities, Affiliates located in Asia-Pacific, Europe, and North America, and individual members from around the world.
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ISPE is an individual membership Society of more than 18,500 professionals in 90-plus countries involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE membership.

We appreciate the opportunity to submit these comments for your consideration.

Sincerely,

John E. Bournas
CEO & President, ISPE

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

Comments from:

Name of organisation or individual
International Society for Pharmaceutical Engineering (ISPE) 7200 Wisconsin Avenue, Suite 305 Bethesda, MD 20814 USA +1 301-364-9210 regulatorycomments@ispe.org Transparency Register # 316626227774-56

General comments

General comment (if any)

We suggest that it is unnecessary to distinguish between RABS and Isolators as there is a significant difference between them in respect of aseptic performance. The draft is confusing in mixing reference to each of the types. To enable greater clarity, the requirements for RABS and Isolators would best be specified individually.

Proposed change:

Show the specific requirements of the two different types individually in Section 6: Equipment.

The terms “Risk Assessment”, “Risk Management” and “QRM Principles” are used throughout the document and it is unclear how these should be interpreted. We suggest to, standardize use of terms associated with risk throughout document to one of the following:

- Risk assessment - a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. (Note: this aligns with ICH Q9 glossary)
- QRM principles – application of data, SME knowledge, and output of quality risk assessment to make risk-based decisions or use a risk-based approach
- Risk – general application of the word. Per ICH Q9, risk is the combination of the probability of occurrence of harm and the severity of that harm.

Provide in the glossary definitions of the terms in the sub-bullets above to ensure no ambiguity.

Include clarity that the Contamination Control Strategy should outline the minimum expectations for execution of risk assessments. These risk assessments would then inform the risk-based decisions associated with topics that Annex 1 requires QRM principles to be used for along with any additional applicable data or knowledge.

Proposed change:

Include a reference in the text and a definition in the glossary and/or provide a reference list with onward reference to ICH.

It is much appreciated that the revised Annex1 provides a much more detailed explanation of aseptic production areas, technology and processes compared to the current document.

Suggestion:

Please specify the requirements for the three aseptic production options:

- conventional classified rooms
- RABS
- Isolators.

We feel the guideline would be more user-friendly if the requirements are clearly listed as:

1. Common requirements for all three options.
2. Specific requirements for the chosen option – included as a section for each option; including, for example, differentiated monitoring requirements for conventional clean rooms vs. barrier technologies; etc.

The item includes a reference to non-sterile products: ‘principles and guidance … products that are not intended to be sterile (such as….); and this raises uncertainty. We feel that it is not clear to the industry or the inspectors which

General comment (if any)
of the described expectations and requirements are to be implemented, or how. The concern is that this will lead, through potential inspection findings/observations, to over-specification and the implementation of unnecessary requirements. **Proposed change**: As Annex 1 is the only GMP document that defines grades, other Annexes could be cross referenced to Annex 1.

General comment (if any)

Throughout the document, the terms ‘contamination’, ‘contamination control’, and ‘contamination control strategy’ are used to describe all microorganisms, pyrogens and particulates and associated controls. Not all microorganisms, pyrogens and particulates are due to contamination events nor should they be regarded as contaminants. Microorganisms, pyrogens and particulates may inherently and routinely exist in materials and environments and not represent a hazard to product quality. The term ‘contamination’ should be used for an undesired quantity or type of microorganisms, pyrogens and particulates which represent a direct hazard and risk to product quality. This distinction would assist in the objective and effective application of risk assessment and quality risk management. Both 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 require control; however, their control, level of tolerance, means of measurement, the assessment and response to their presence are necessarily different.

Throughout the document distinction should be made between ‘contamination’ and/or ‘contamination control’ - 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. A single control strategy 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:

Remove the terms ‘contamination’ and ‘contamination control’ where these have been applied to microorganisms, pyrogens and particulates which are not hazards to product quality. Remove the term ‘contamination control strategy’ and replace with ‘microbial and particulate control strategy’.

Include a definition of ‘contamination’ in the Glossary which is aligned to ICH Q7A

‘The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens), or of foreign particle matter, into or onto a raw material, intermediate, drug substance or drug product during production, sampling, packaging or repackaging, storage or transport’ with the potential to directly adversely impact product quality’

Add a Reference list in the Annex which mentioned ICHQ10 and includes 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.’

Throughout the document, not all aspects of validation are applicable at each phase of development. For the guidance in this document related to validation sites that manufacture Investigational Medicinal Products should apply Quality Risk Management principles to clearly define validation expectations for each phase of clinical development.

Proposed Change:

Refer to Annex 13 for Investigational products for clarity

It is suggested that EMA should introduce the concept of “Contamination Recovery Rate”

Proposed change:

General comment (if any)

Incorporate the concept in the Annex and add the definition of “Contamination Recovery Rate” to the Glossary

There was a general expectation from responses received that the document would be clear, concise and not open to interpretation, with a readily accessible, straightforward format and clarity in what is mandated and what is risk reviewable. This is felt to be particularly important now that QRM is a major decision driver; and given that many that refer the document have English as a second language. Examples include:

- Indeterminate use of English modal verbs creating concern for readers using English as a second language; for example, the use of “shall” and “should” is less readily understood than “is to”, “will” or “must” where something is mandated. For example, “shall” has a US Supreme Court judgement that determines that it is equivalent to “may” and, so, is legally not an obligatory expectation.
- Definitions appearing at the start of some topic paragraphs yet not at the start of the next topic paragraph

Proposed changes:

Whilst it is not proposed to significantly alter the structure it is suggested that an overview is taken of the format to bring each topic in line with a standardised paragraph structure together with a more positive use of English

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Examples include:

- Provide what is mandated using, say, bullet points with those areas that are to use a risk review format to determine following
- Use more determinate language
- The Glossary could incorporate all definitions in the document and reference to it made throughout the text.

Unless, overlooked by the reader, there is no guidance on the outward track of waste from the process. All is focused on the feed into and continuation of the process and not its by-products…. For example. Can bagged waste be transferred out of a Grade B environment direct to, say, CNC as long as, say, there is a unidirectional interlocked outward airflow through a transfer hatch or MAL or should it be to “C” and then to CNC or Unclassified? This is significant for, for example, small ATMP facilities

Proposed change:

Include a section on the removal of wastes from steriles areas

Generally, pyrogen and endotoxin terms seems to be being used synonymously which leads to confusion. Bacterial pyrogens include endotoxins and exotoxins, although many pyrogens are endogenous to the host. Endotoxins include lipopolysaccharide (LPS) molecules found as part of the cell wall of Gram-negative bacteria, and are released upon bacterial cell lysis

Proposed Change:
Use the Glossary to clarify

The use of Levels and Limits appear interchangeable and should be standardized.

Proposed change:
Incorporate definitions in Glossary

The naming convention for Grade A or Grade B and “Aseptic Processing Area” and “Sterile Core” are used interchangeably and should be standardized, or defined in the Glossary.

Chapter 7
We suggest for WFI and Pure steam comply with Pharmacopoeia monographies for feed water and production.

General comment (if any)
Could GMP’s in Annex 1 address regulators expectations in terms of storage and distribution including requirement for control and monitoring for such systems. Could annex 1 include requirements for WFI storage and distribution control and monitoring at cold temperature below 70°C based on QRM. Use of cold WFI is required in some processes and need to be assessed to allow these processes. Industry requires some flexibility and guidance’s from regulator to handle their water system. We suggest having possibly different requirement regarding water systems using distillation processes and systems using Reverse osmosis as first production stage.

Specific comments on text

Document map

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')*
2-3	Comment: Would be better to call it contents or index. "Additional areas" in 1 Scope not understood. Proposed change (if any): Cross reference with other annexes
3	Comment: It would be better to have a separate section for APS as it is a specific simulation. Section 9 apply to Environmental monitoring and Aseptic Process Simulation Proposed change (if any): Take APS out of Sect 9 and put it in a new section to make reading easier. Viable and non-viable environmental ~~and process~~ monitoring and Aseptic Process Simulation
3	Comment: The document has an illogical sequence: for example, air grades are defined in section 5 but are referred to in section 4. Need to define Grades A-D early before using references to them. Proposed change (if any): Keep the document organisation consistent with general GMP Guidance, incorporate the definitions of Grade A, B, C and D in the Glossary and refer to the Glossary when mentioning them.
3	Comment: Section 8 has equipment items in it. These should be collected together in Section 6 Proposed change (if any): Consider putting all equipment in the same section or separating specific technologies.

Scope

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')*
6-23	Comment: Scope as an opening section must have clarity of definition. The second paragraph seems open to interpretation and needs clarification. Proposed change (if any): "This guidance considers the manufacture of sterile medicinal products manufactured by both terminal sterilisation and aseptic processing. It covers a wide range of product types, including sterile active ingredients (APIs) and finished dosage forms for both classic "small molecule" and large molecule biotechnology products. In addition to product types, guidance is also provided on batch sizes (single unit to multiple units); campaign working (single batches to campaigns comprising sequential batches); manual processes to highly automated systems; and primary packaging materials and certain specialised manufacturing technologies.

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')*
	The manufacturing environment is also considered, including cleanrooms, RABS, and isolators, and their relationship with open and closed process systems. This Annex provides general guidance that should be used for all sterile medicinal products, investigational medicinal products and sterile active substances~~, via adaption,~~ using the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and ~~pyrogen~~ endotoxin contamination associated with microbes is prevented in the final product, and to ensure more broadly that the products consistently meet their quality attributes of potency, purity, sterility, and identity. Other important GMP principles, such as cross-contamination control for example, are addressed elsewhere in the GMP guidelines and annexes. The intent of this Annex is to provide guidance for sterile medicinal products. However, some of the principles and guidance, such as contamination control strategy, cleanroom classification, qualification, monitoring and gowning, may be used to support the manufacture of other products that are not intended to be sterile. Examples include some liquids, creams, ointments and low bioburden biological intermediates ~~but~~ where the control of microbial, particulate and endotoxin contamination~~, to reduce it as far as possible~~, is considered important.”
9-10	Comment: “single unit to multiple unit” seems unclear and needs clarification. Proposed change (if any): Suggest incorporating in Glossary “Multiple unit” and “Single unit” definitions

Principle

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')*
36	Comment: “Attitude” is a term that is vague and not defined. Distribution processes are not directly linked to sterility. For distribution, consider GDP guidance and make relevant link for sterile products. This may be considered for Cold chain maintenance Proposed change (if any): Incorporate “attitude” in Glossary or delete the term: “Personnel must have appropriate qualification, skills, **and** training ~~and attitudes~~ with specific focus on the principle involved in the protection of sterile product during the manufacture, packaging and ~~distribution processes.~~”
41	Comment: “Commissioned and Qualification” are very close in meaning, so “commissioned” can be deleted. The guide must give more information on personnel, should be considered as a team and not one person. Proposed change (if any): “Process and monitoring systems for sterile product manufacture must be designed ~~commissioned,~~ qualified and monitored by a team ~~personnel~~ with appropriate process engineering, and microbiological knowledge.”
44-48	Comment: The Annex 1 draft describes that QRM principles apply to processes, equipment, facilities and manufacturing with

<table>
<tr><th>Line number(s) of the relevant text</th><th>Comment and rationale; proposed changes
(If changes to the wording are suggested, they should be highlighted using 'track changes')</th></tr>
<tr><td></td><td>the use of Risk Assessments for justifications to alternative approaches “only if these alternative approaches meet or surpass the intent of this Annex”.

Proposed change (if any):
Change wording to: “only if these alternative approaches at least meet the intent of this Annex”</td></tr>
<tr><td>51-53</td><td>Comment:
We certainly acknowledge the importance and need to consider contamination controls across a facility. We believe that the effectiveness of all controls in a facility should be evaluated, and that contamination controls are a part of that. However, there is a risk of missing the holistic picture across all controls which the annex otherwise talks to, so we propose a rewording.

Proposed rewording:
“Quality Assurance is particularly important, and manufacture of sterile products must strictly follow carefully established and validated methods of manufacture and control. A contamination control strategy should be implemented across the facility, and the effectiveness of contamination controls and other control and monitoring measures should be evaluated. <s>In order to assess the effectiveness of all the control and monitoring measures employed.</s> This assessment should…”</td></tr>
<tr><td>60-62</td><td>Comment: The use of “these” in this sentence seems to be referring to two different aspects, the control measures and the sources.

Proposed change (if any): Modify the sentence as [60] “These sources are typically assessed…”</td></tr>
<tr><td>69-107</td><td>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 indicate 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):
Quality systems and respective elements that must be considered within the control strategy are tabulated below:

<table>
<tr><th>Quality System</th><th>System Content (includes but not limited to)</th></tr>
<tr><td>Facility</td><td>Design, traffic flows, utilities, maintenance preventative and repair, cleaning, disinfection, monitoring systems</td></tr>
<tr><td>Manufacturing Process</td><td>Design, equipment, in-process controls, in-process tests</td></tr>
<tr><td>Personnel</td><td>Training, certification, garbing,</td></tr>
<tr><td>Procedures</td><td>Vendor approval, out sourcing, risk assessments, trending, analysis, investigational tools, CAPA, continuous improvement</td></tr>
<tr><td>Product</td><td>Raw materials, in-process tests, end product tests, containers, closures</td></tr>
</table>
</td></tr>
</table>

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')*
69	Comment: What does “Documented contamination control strategy” mean, and what is the scope? Proposed change: Suggest adding definition of “documented contamination control strategy” in Glossary
112-117	Comment: Add clarity such as a note near Annex 1 draft lines 112 and 117 that provides guidance around what are the appropriate sections from Annex 1 that should be taken into account for manufacture of biological medicinal products to clarify expectations from the cross reference in Annex 2 Part A Section 6 and associated footnote 18. Proposed change (if any): As this point is implemented in the scope with non-sterile or low bioburden product, add reference linked document Annex 2 / 9 / 10 / 13 / 14 /
117-123	Comment: Add reference in Reference list described above

Pharmaceutical Quality System (PQS)

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')*
145-152	**Comment:** Specification of risk assessment considering microbial and chemical contamination. Include guidance regarding the approach to be taken to complete an effective risk assessment that can accurately quantify the level of product contamination. [45] QRM is defined as proactive tool – review of risk assessment during product quality review is a retrospective way of review. **Proposed change (if any):** d) Risk assessment is performed to identify, assess, eliminate (where applicable) and control contamination risks to prevent microbial and chemical contamination, to monitor and detect contamination, and to establish process requirements and acceptance criteria for all elements of a sterile manufacturing process. [148] Fundamental mechanisms of product contamination by airborne deposition, surface contact or liquid transfer as well as fundamental risk factors that relate to product contamination such as exposure area and time and the number of contacts with contaminated surfaces should be taken into consideration. [148] The risk assessment should be documented and should include the rationale for decisions taken in relation to mitigating risks, discounting of potential risks and residual risk. The risk assessment should be reviewed regularly as part [151] of on-going quality management and during change control ~~and during the periodic product quality review~~.
159	**Comment:** Missing the word “for” in the sentence.

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): f) Persons responsible for the quality release of sterile medicines…
167	**Comment:** Such excursions are not necessarily non-conformances. It needs to be distinguished between Grade A/B and or C/D and process, e.g. in Aseptic Processing C/D is of less criticality, in terminal sterilization C/D are of different purpose. In that the related process for an area needs to be addressed. Language such as in USP is suggested to replace the above cited text: ….out of environmental control excursions **Proposed change (if any):** 3.2 Investigations should be performed into non-conformities, such as sterility test failures or [167] environmental control excursions or deviations from established procedures, with a …
168	**Comment:** Investigations should cover microbial as well as chemical contaminations. **Proposed change (if any):** …specific focus regarding the potential impact to ~~sterility~~ microbial and chemical contaminations, to not only the specific batch…

Personnel

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')*
181-182	**Comment:** Requirement does not differentiate between Class A grade clean rooms used for product processing and ancillary support background Class B/C cleanrooms. Background cleanrooms may not require minimum and maximum number of people. Should be based on QRM. **Proposed change:** "The maximum number of operators in critical areas should be determined and documented based on QRM principles, ~~documented in the contamination control strategy,~~ and validated."
188-194	**Comment:** Are these requirements intended to include monitoring of individuals operating and cleaning Grade D rooms? **Proposed change (if any):** "All personnel (including those performing cleaning and maintenance) in ~~such~~ critical areas [….]"
196-208	**Comment:** Grade A/B is confusing. **Proposed change (if any):** Replace "Grade A/B" by "Grade A & B"
203-206	**Comment:** 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). ***upon each exit from the clean room***" This is implying that personnel are to be microbial monitored upon

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')*
	each and every entry and exit into / from a clean room. **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 [206] ~~upon each exit from the cleanroom~~ "for personnel conducting critical interventions and testing frequency based on risk assessment."
203	**Comment:** This goes too far because this condition excludes any other entry to Grade A/B rooms even outside manufacturing times. **Proposed changes:** "Only trained personnel who have passed the gowning assessment and have participated in a successful aseptic process simulation (APS) test, during which they performed their normal duties, should be authorized to enter any grad A&B area, in which aseptic operations ~~**will** be conducted, or~~ are being conducted, whilst unsupervised."
206-208	**Comment:** The term continuous monitoring is confusing with regards to personnel monitoring as used in the sentence: It may be understood as covering routine monitoring. If this is not the intent, it should be clarified. The suggested change below is to the wording and is considered aligned with the requirements in 9.26/line 1724-1726 **Proposed change (if any):** [207]"It should be noted that there should also be an ongoing routine ~~continuous~~ monitoring program for personnel including some consideration of periodic monitoring under the supervision of the quality unit."
217-220	Comment: The statement needs more clarification. External staff without training (and without periodic health checks as required in 4.7) should anyway not be brought into grade A/B areas (possible only after downgrading of the A/B area during a complete shutdown, refurbishments etc.). Is this requirement also valid for other clean areas? (C, D)
222-226	**Comment:** We propose to delete the sentence "*periodic health check should be performed*". As the personnel are to be instructed to report any health conditions which possess a risk to the product quality, a periodic check will not add extra value. The check will only give a picture of the current health status, and will be of no value if for example the employee gets an infection shortly after the check is performed. In addition to this all the employees should at all time behave in agreement with proper aseptic behaviour, and would also by this minimise any risk of contamination of the product. **Proposed change (if any):** "High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to 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; ~~periodic health checks for such conditions should be performed.~~ Actions to be taken …"

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')*
228	**Comment:** What are the expectations of the "designated competent person"? This should be by a person or group with the appropriate microbiological training. **Proposed change (if any):** We suggest giving a definition of "competent person"
236-237	**Comment:** Although understandable that personal items such as mobile telephones may be a source of contamination, the requirement of not having mobile phones in the clean areas may limit opportunities for normal work related communications. Therefore, it is proposed to be re-phrased to allow - under proper precautions – necessary work related phones. It should rather be based on an evaluation of the activities, processes, handling etc. that takes place, i.e. using QRM-principles. Mobile phones should be allowed under proper precautions, e.g. in plastic bags or dedicated production phones is acceptable. **Proposed change (if any):** "Wristwatches, make-up and jewellery and other personal items ~~such as mobile phones~~ should not be allowed in clean areas. **However, necessary work related items, e.g. company dedicated mobile phones, may be allowed if justified by a risk based approach incl. under necessary precautions"**
241	**Comment:** Doing an integrity checks prior to entry of the cleanroom may jeopardize the gowning. One needs to focus on correct gowning (e.g. not touching the floor etc.) once gowned you don't want the operator to stretch and contact surfaces. For this reason, uniform inspection (integrity) should be done during laundry and restocking but not immediately before room entry. Also, the word 'integrity' indicates a thorough intense check as the term integrity is used elsewhere in a different context (e.g. CCIT) **Proposed change:** "Garments should be visually checked for cleanliness **and being intact** ~~**integrity**~~ prior to entry"
244	**Comment:** For the replacement frequency to be qualified and qualification is a precondition to use for commercial, how is this expected to be accomplished. The frequency should be established and then through the monitoring if it is not frequent enough it should be adjusted. **Proposed change (if any):** [244]at a set frequency ~~determined by qualification or~~ if damaged is identified
253-272	**Comment:** Even if this section comes from existing Annex 1, the requirements to clothing is very detailed, where the general trend for the new Annex 1 is to use QRM to ensure that the controls are suitable to the intended situation and risks (e.g. contamination). In general, we propose that the section is reduced in specification, and emphasis made on minimum gowning and use of QRM for the specific situation and based on knowledge of your process, equipment and area. Additional comment recommend providing guidance on best gowning practice in Grade C/D area immediately adjacent to the

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')*
	isolator. **Proposed change (if any):** ~~a) Grade D: Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.~~ ~~b) Grade C: Hair, beards and moustaches should be covered. A single or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected or sterilized shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.~~ ~~c) Grade A/B: Sterile headgear should totally enclose hair and facial hair; it should be tucked into the neck of the sterile suit; a sterile face mask and sterile eye coverings should be worn to cover all facial skin and prevent the shedding of droplets and particles. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.~~ Garments should be packed and folded in such a way as to allow operators to change into the garments with contact to the outer surfaces of the garment reduced to a minimum. **The description of clothing required for each grade should be commensurate with the risk in the area and based on QRM-principles. As a minimum, clothing, footwear and headgear should be sterile and covering the full body and face in grade A/B.** **The intent of the QRM should include assessment of the production process(es), the purpose of the area, the necessary degree of product protection etc. which determines the requirements to e.g. retaining particles, levels of particle shedding, reduction of contamination in the area.** **The following elements can be taken into consideration in the assessment: what should be covered (e.g., hair, beard, moustache, skin), protective suit (one or two pieces' suit) sterile for the critical areas , shoes (dedicated or shoe cover), measures to avoid contamination from outside the clean room and available relevant data for the area.** Garments should be packed and folded in such a way as to allow operators to change into the garments without contact to the outer surfaces of the garment reduced to a minimum.
276	**Comment:** Socks are not the only source of contamination consider pieces of garment potential sources of contamination and locate properly the place to wear these pieces of garment. **Proposed change (if any):** "Outdoor clothing should not be brought into changing rooms leading to Grade B and C rooms. It is recommended that factory uniforms and non-linting socks or cleanroom undergarments be worn before entry to changing rooms for Grade C and B areas. Where clothing is reused this should be considered as part of the qualification."
281-284	**Comment:** Clarified what is a "work session"? Might be considered as a shift? **Proposed change (if any):** We suggest incorporating a definition of "work session" in the glossary
283-284	Comment: agreeing that garments and gloves should be changed at least for every working session, not only for the Grade A/B area, but also for aseptic personnel working in grade C/D area immediate adjacent

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')*
	to the isolator or RABS. Proposed change (if any): Make clarification for personnel gowning immediate adjacent to the isolator or RABS that is not grade A/B.
291	**Comment:** Integrity is a misleading term as it is used in stronger meaning at different situations, e.g. CCIT or package integrity **Proposed change:** "After washing and before sterilization, garments should be checked for being intact ~~integrity~~."
293-301	**Comment:** The portion; "Operators performing aseptic operations should adhere to strict aseptic technique at all times. To prevent changes in air currents that introduce lower quality air, movement adjacent to the critical area should be restricted and the obstruction of the path of the unidirectional airflow must be avoided." Is not clear **Proposed change (if any):** Suggest changing to "To prevent changes in air currents that introduce lower quality air in Grade A, movement adjacent to the critical area should be restricted and the obstruction of the path of the unidirectional airflow must be avoided."

Premises

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')*
305	**Comments:** EMA inspectors have been insisting on separation of material and personnel airlocks. If this is a requirement it should be outlined here. Suggest "Separate airlocks for materials/equipment from those for personnel are preferred, as appropriate"
308	**Comment** Filters of "Appropriate efficiency" is not defined. **Proposed change:** We suggest "(e.g. Minimum of F9 for Grades D and C, minimum of H-13 for Grade B, minimum of H-14 for Grade A)"
314	**Comment/rationale:** To clarify the concept, adding the correct reference (i.e. the table 3, 4 and 8.10) Add "as defined in table 5"
320 and generally	**Proposed Change:** The word "laminar" should be replaced by "unidirectional" (see below comments to 2177 – 2178)
318-332	**Comment:** "stopper bowls, open ampoules and vials," is too prescriptive and does not adequately describe the risk. **Recommended Change:** Replace "stopper bowls, open ampoules and vials," with the less prescriptive "open product contact parts". Comment: Replace "homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value)" homogeneity is not defined and not applicable since non-uniformity is often required to assure correct flow patterns. Further, the velocity recommendation, while historical, is not scientifically supportable and has been shown to be excessive by repeated studies. ISO 14644-4 suggests velocity as low as 0.2m/s are appropriate for ISO-5. Protection of the critical zone is of greatest import, velocity is only a surrogate measure intended to prove that a verified airflow pattern is still in place. By itself, velocity is not a

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	meaningful acceptance criterion. Recommended Change: Delete "homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value)", replace with "a protective flow of clean air from the HEPA filter, across the critical zone and towards areas of lower classification with velocity measured at critical points which is clearly justified and aligned with airflow visualization studies (historical guidance value of 0.36-0.54m/s on average – lower velocities are often required to minimize turbulence)" Replace "close to the terminal air filter face" with "10-15 cm from the filter face" as more specific and consistent with best practice. Replace "at the working height" with "at a user defined distance proximal to the working height" as consistent with FDA and more scientifically supportable since turbulence within 30cm of a flat surface commonly makes velocity impossible to measure consistently. Deleted the word "validated" from "The maintenance of unidirectional airflow should be demonstrated and validated across the whole of the grade A area." Airflow visualization does not rise to the level of validation.
334-338	**Comment/rationale:** The guidance that "only Grade C cleanrooms should interface with a Grade B aseptic processing area" is not online with prior guidance and facility designs aligned with that guidance. This sentence does not recognize the difference in risk between materials and personnel entering a facility and those exiting, as was made clear in prior versions of the annex. **Proposed Change:** Suggest editing to "For open aseptic operations, grade B is background environment for grade A aseptic preparation and filling. Grade B is also used for storage and transfer of sterilized and protected components or for higher risk, non-sterile operations. Access to grade B should normally be directly from grade C. Grade D and CNC may serve as entry to Grade B via separative devices such as washers, autoclaves and pass-thru boxes, as justified by quality risk management. Materials and personnel may exit Grade B directly to Grade D and CNC" with appropriate cascade pressure airlock"
340	**Comment/rationale:** It is said that Grade C and D are clean areas for carrying out less critical stages in the manufacture of sterile products; the sentence can be misleading if no reference is made to paragraph 8.10 **Proposed change**: Grade C and D are clean areas for carrying out less critical stages ~~in the manufacture of sterile products~~ (see paragraph 8.10)
343	Delete the word "unbroken" joining of dissimilar materials and allowance for expansion are essential requirements for construction. Suggest substituting the words "flush, to the extent practical". Excessive caulking of small interfaces to produce a "smooth" surface is a source of particulate and undesirable.
351	**Comment/rationale:** While the intent of minimizing fibers in cleanrooms is laudable, the language of this sentence is not practical, as it suggests a moratorium on fibrous materials – which includes all fabrics, filter media, etc. **Proposed Change:** We suggest replacing "should not be permitted" to "should be minimized to the extent practical. Fragile natural fibres (e.g. cotton, wool) should be avoided. Where fibrous materials are used, they should be selected to minimize shedding."
353	**Comment/rationale:** Suggest removing the word "false" as it creates confusion regarding what ceilings might be exempted from this requirement. Replace "prevent" with "work with HVAC to minimize" as ceiling construction works with HVAC and pressurization to control the ingress of contaminants. The word prevent suggests that ceilings should be hermetic, which is neither required nor practical in many cases. **Proposed Change:** Remove the word "~~false~~ ceiling". Replace the word "prevent" with "minimize (when considered with the pressurization)".

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356	**Comment/rationale:** We agree in principal, but feel that this comment does not sufficiently clarify the need to drain fluids in Grades A and B. Indirect drains are sometimes needed within isolators, for example where washing is required as part of pre/post process. Of course, during operation when the area is grade A/B drains are sealed closed, but are "present" anyway. This kind of wording seems too much radical. While aseptic processing is implied, we suggest adding the word "aseptic" **Proposed change:** Add "aseptic" ahead of "grade A/B" Add "Where sinks and drains are needed for pre or post process phases, they should be indirect drains, not directly connected to sanitary waste lines and must be sealed closed during operation." Suggest replacing "traps and water seals" which are synonyms with "adequate means" which does not specify a technology and allows for numerous other solutions.
357	**Comment/rationale:** Drains in Grade C can also contribute to microbial contamination, especially if directly connected to sanitary sewers and not sealed. **Proposed Change:** Suggest adding "drains in Grade C should be sealed between uses, wherever practical."
361 - 367	**Comment:** The wording "typically airlocks used for personnel movement are separate to those used for material movement." is unclear. Lack of this separation appears in numerous inspection citations, without clear rationale or justification for this separation (or lack thereof) **Proposed Change:** "airlocks used for personnel gowning should be separate from those used for material cleaning/disinfection, due to the difference in duration and operations for these transitions; unless otherwise justified appropriate strigent procedures where the risk has been assessed. **Comment:** The wording of "final stage" in the sentence: "The *final stage* of the airlock should, in the at-rest state, be the same grade as the area into which it leads." Is not clear. **Proposed changes:** Replace "the final stage of the airlock" with "the area of the airlock immediately adjacent to the door to the cleaner room" or "the downstream end of the room" **Comment:** There has been significant confusion in the industry as to the meaning of: "The final stage of the airlock should, *in the at-rest state, be the same grade as the area into which it leads*." We read this as meaning that a Grade C airlock (which is ISO 7 at rest) may lead into a Grade B room (Which is ISO 7 in operation); however, many practitioners do not trust that this is the intent of this sentence. **Proposed Change:** Revised text "The area of an airlock adjacent to the door should, in the at-rest state, attain the same ISO classification as the area into which it leads achieves in the in-operation state. (e.g. a Grade C airlock may lead into a Grade B room)" **Comment:** Solidify the wording of: "The use of separate changing rooms for entering and leaving *clean* areas is *generally*

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	desirable." **Proposed changes:** Change the wording of the sentence to "The use of separate changing rooms for entering and leaving aseptic Grade B/A areas is desirable. Where this is not practical, temporal separation by SOP may be considered." Add "where the risk of cross-contamination is high, separate changing rooms for entering and leaving Grade C areas may also be desirable, as identified using QRM principles".
276-279	**Comment:** "It is recommended that facility suits, including dedicated socks be worn before entry ….". The addition of dedicated socks will be a significant change for industry. Is their data to show that socks are a major source of contamination? **Proposed change (if any):** It is recommended that facility suits, be worn before entry. Contamination from socks should be controlled and socks should be worn under dedicated plant shoes....
369	**Comment:** Personnel entry and exit risks are different. **Proposed change:** Add the word "entry" after the word "personnel" "A cascade concept should be followed for personnel entry"
365-366	**Comment:** Grade is ambiguous as which part of the grade should be used. **Proposed change (if any):** The final stage of the air lock should, in the at rest state, be the same as the in-operation state as the area into which it leads.
375-377	**Comment:** The moratorium on Pass-through hatches without active filtered air supply is, to the best of our knowledge not supported by data or study. A simple numerical evaluation of maximum contamination transfer shows that a passive pass=thru does not show any meaningful contamination. We suggest a more nuanced risk- based approach (see attached article on the design of pass-thru hatches.) Unventilated Pass-through hatches are most appropriate when they are small in volume (<1m^3), used for transfers crossing a single classification boundary without containment needs and infrequently used (<6/hr) For higher risk installations, pass-throughs can be either passively ventilated with transfer air through controlled leakage from adjacent rooms via room pressure difference, or actively ventilated via extraction of room air or HEPA filtered air supply/recirculation. Active ventilation should be considered for large pass-throughs or pass-throughs which bridge across multiple classifications (e.g. from Grade D to Grade B). Provisions and procedures should be developed according to risk management principles to minimize the risk of contamination (e.g. by the incoming material or by entering air). Time delays which restrict the opening of the doors, to minimize the migration of particles and to allow sanitizing agents sufficient contact time, should be considered.

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	Proposed Change: "Pass-through hatches should be designed and justified using quality risk management principles. Risk assessment should consider the direction of material flow, the classification difference between spaces, sanitization methods, frequency of use, containment needs as well as contamination and cross-contamination risk.
379	**Comment:** The statement "Only materials that have been…" seems unnecessarily specific, and could lead to over interpretation, e.g. it could mean that you can transfer an 8mm AISI304 bolt into the area, but not a 10mm AISI316 bolt **Proposed change proposed change (if any):** For airlocks leading to grade A and B areas, only **types of** materials and equipment that […]
379-388	**Comment:** The purpose of this paragraph is unclear. The statement regarding "maintaining continuity" seems superfluous. The need for the cleaning of materials and equipment transferred into Grade A/B to be either validated, or assessed and monitored is a valid point, but not clearly made. **Proposed Change:** Remove [381] "the continuity of grade A should be maintained in the aseptic core when the materials have to be transferred from grade B to grade A areas"
390-91	**Comment:** "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." Doesn't this apply to all transfers in all cases and Grades? **Proposed Change:** "The movement of material from less clean to more clean areas should be based on QRM principles, with cleaning and disinfection commensurate with the risk of microbial, particulate, pyrogen, or cross-product contamination"
394	**Comment:** As written this will require facility upgrades (should be prevented) – visual/audible indicators are common in this application – is there evidence that this is a quality concern? **Proposed Change:** 5.10 "Both airlock doors should not be opened simultaneously. The opening of more than one door at a time should be prevented, at least a visual and/or audible warning system should be operated. The impact of the time between the closing and opening of interlocked doors should be evaluated and, where required to maintain segregation, a time delay should be established in the interlock system."
400-402	**Comment/rationale:** The requirement and recommendation for application of terminal filter by area classification is unclear. The required level of filtration to achieve ISO 8 for 0.5 micron particles is not usually a HEPA. This paragraph seems to suggest that ULPA filters may be required. However, the stated airborne total particle and viable limits can be achieved using HEPA filtration (H-13 or H-14).

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	Proposed Change: Refer to recommendation at 308. A HEPA is required to achieve Grade A and B, and optional at Grade C. Remove mention of ULPA as these filters are acceptable, but not required. **Comment/rationale:** [400] Maintenance of a pressure differential and an airflow requires that the doors between spaces be closed. When a door or other large opening is present a pressure differential is difficult, if not impossible, to maintain. FDA includes a statement that pressure targets are with doors closed. Furthermore, continuous processing devices which use an opening between classified areas, such as a depyrogenation tunnel may not provide the target pressure difference across the open face of the tunnel. **Proposed Change:** [400] Revise "filtered air supply should maintain a positive pressure and an air flow" to "filtered air supply should maintain a positive pressure (with doors closed) **and/or a directional** air flow".
405-410	**Comment/Rationale:** These sentences are unclear and cause some misinterpretation. Suggest being more specific. Also, this sentence doesn't address the design of these alternate pressurization schemes. The need to disinfect spaces is universal in aseptic processing. However, the need to disinfect anything upstream of the HEPA filter is extremely rare. HEPA filters at H-13 are nearly absolute in their retention of viable organisms (See ASHRAE Paper _____) disinfection of the upstream side of the filter should only be used in highly pathogenic production. This section seems to suggest that disinfecting HVAC is necessary. **Proposed Change:** "The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities, e.g. the clean rooms and HVAC, and the treatment of air leaving a clean area may be necessary for some operations." Change to "The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. **Cascade pressure relationships may be supplemented with pressurized or depressurized airlocks or corridors. Where containment requires air to flow into a critical zone, the source of the air should be from an area of similar classification. Disinfection** of facilities, e.g. the clean rooms, **HVAC downstream of supply HEPA filters**, and the treatment of air leaving a clean area may be necessary for some operations."
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):** Air flow patterns should be visualised in grade A/B areas to evaluate if airflow is unidirectional in grade A and there is no air ingress from grade B to grade A.

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415-417	**Comment:** The suggestion of unidirectional flow in Grade B is excessive and not required to achieve desired particle concentrations. **Proposed change (if any):** Air flow patterns should be visualised in grade A/B areas to evaluate if airflow is unidirectional in grade A and there is no air ingress from grade B to grade A.
417	**Comment:** Smoke Studies to demonstrate that air flow patterns are appropriate can be used to qualify unidirectional flow regimes – e.g. “grade A”, “grade A environment”,” grade A supply”. In other areas Smoke Studies can be used as a diagnostic tool - for example to determine the cause of unexpected high recovery time - but in turbulent flow regimes airflow patterns cannot be subject for qualification as there can be no clear acceptance criteria. Furthermore, the prevailing flow regime in B is “turbulent” – clean-up is achieved by dilution, not by ‘piston effect’ as in grade A. Make recording of airflow pattern mandatory – inspectorates expect to see the recordings and the companies can utilise them in a number of ways spanning from training over preparation for procedural changes to trouble shooting. **Proposed change (if any):** Air flow patterns should be visualised in grade A~~/B~~ areas to evaluate if airflow is unidirectional. Where unidirectional air flow is not demonstrated, corrective actions, such as design improvements, should be implemented. In ~~the~~ other areas ~~**with unidirectional flow (grade A air supply),**~~ the need to demonstrate the air flow patterns should be based on a risk assessment. Video recordings of the airflow patterns are ~~recommended~~ **mandatory**. The outcome of the air visualisation studies should be considered when establishing the facility’s environmental monitoring program.
419	**Comment:** Industry practice is to perform airflow visualization both at-rest and in-operation (static and dynamic). This allows comparison of performance prior interventions with conditions during interventions. **Proposed change (if any):** “performed under **static (where required) and** dynamic conditions” Add “Static” to the glossary.
425-426	Comment: The pressure differences should be recorded regularly or otherwise documented. Proposed change (if any): Use the proposed requirement from WHO 11.11 “pressure differentials should be regularly recorded and failure alarmed”
428-431	**Comment/rationale:** The phrase “*...remote camera access with a complete view of the area..*” could be in contrast with local legislations. In Italy, for example, law forbids filming the operators at work. Please keep highlighted this could impact legacy facilities.
428-431	**Comment:** Clarify what is meant by “clean areas” **Proposed change (if any):** Change the sentence to: “Consideration should be given to designing facilities that permit observation of activities from outside the **aseptic areas**, e.g. through the provision of windows or remote camera access with a complete view of the area and processes to allow observation and supervision without entry.”
433	Heading

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	Comment: As the Technologies dealt with in this section are considered to be for production purposes it should be stated specifically in the heading. For example, there is no need for having unidirectional air flow in a sterility test isolator **Proposed change (if any):** Heading: Barrier Technologies **for production purposes**
435,456	**Comment**: Isolators & RABS are discussed throughout. Definitions are in glossary however difficult to determine technical difference between "Open Isolator" and "RABS". Could lead to confusion. **Proposed change:** Clarify. Include various types of RABS definitions in Glossary;
437-439	**Comment:** Most commercial aseptic filling processes require transfer of materials into or out of the isolator or RABS enclosure. We agree that transfers into a RABS or isolator are potential contamination sources; however, the suggestion that addition of materials after "sterilisation" is undesirable is impractical in the extreme. Furthermore, the use of the term "sterilisation" in the case of RABS is inaccurate, as 6 log reduction of viable contamination is not proved in these units. Even isolator VHP cycles are better characterized as "disinfection" **Proposed Change:** "The transfer of materials into and out of the RABS or isolator is one of the greatest potential sources of contamination and therefore the entry of additional materials following sterilisation should be minimized." Change to "The transfer of materials into and out of the RABS or isolator is one of the greatest potential sources of contamination and therefore the entry of additional materials following sterilisation should be **carefully designed so that risk of contamination is** minimized.
441	**Proposed change:** Additional wording after 441**: "***ie. Appropriate decontaminant agent, door access event record, positive pressure from enclosure to surrounding area, additional monitoring of contact product surface, additional sterility testing samples)"*
453-454	**Comment:** "Negative pressure isolators should only be used when containment of the product is considered essential. **Proposed change (if any):** Should be changed to double wall isolators that provide both protection of product and containment.
450-451	**Comment:** Turbulent air flow is seen on occasion in RABS as well as closed isolators. Examples where turbulent airflow can be observed are near large pieces of equipment, such as stopper bowls, or mouse holes in the RABS and open isolators. **Proposed change (if any):** Under certain circumstances turbulent airflow may be justified when proven to have no negative impact on the product.
449-451	**Comment:** The use of the words "unidirectional" and "Turbulent" are incorrect in this application. The suggested changes to the definitions in this document would help. "Unidirectional" in this application does not mean "Laminar" moving in parallel streams without eddy currents or other turbulence – which would be impossible. Rather it means flow from the clean air source (filter) across the critical zone and out to a less clean area, without refluxing, induction of particles from an operator or activity, etc. Similarly, "Turbulent flow" is an engineering term that refers to the Reynolds number of the fluid. Most flow in HVAC is turbulent, but may be unidirectional for our purposes. The term "turbulent flow" should be

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	dropped in favour of “turbulence” **Proposed change (if any):** Within unidirectional airflow some turbulence is expected, it may be justified when proven to have no negative impact on the product.
456 - 458	**Comment/rationale:** (typing error) “and” should be deleted **Proposed change:** *“where doors may be very rarely opened during processing, ~~and~~ studies should be performed to demonstrate the absence of air ingress”.* For RABS, where doors may be very rarely opened during processing, controls for sterility assurance should be employed, this includes studies to demonstrate the absence of air ingress. appropriate decontaminant agent, door access event record, positive pressure from enclosure to surrounding area, additional monitoring of contact product surface, additional sterility testing samples)”
460 - 461	**Comment/rationale:** Whether an isolator is open or closed is not germane to this point. All isolators are disinfected by gaseous agent. **Proposed change:** Reformulate as follows: “*For positive pressure isolators with decontamination with a sporicidal agent, the surrounding area should correspond to a minimum of grade D*”.
467-470 453-454	Velocity is more important in the containment of particles than flow/unit time. The cited PDA article confuses terms. A measurement of cc/s is a “leak rate” not a “leak velocity”. Velocity is one-dimensional (e.g. cm/s), the stated metric is cubic (cc/s). **Comment/ Rationale:** This document appears to use “disinfection”, “sterilization” , “sanitization”, “decontamination and “bio-decontamination” interchangeably; we recommend using “disinfection” except where a >10^6 reduction is proved, which is “sterilization”. As previously stated, negative pressure isolators are not appropriate for aseptic processing, mention of them should be stricken. As previously stated, introduction of items into an isolator during operation is normal and customary. Only the means chosen for introduction of these items can present a risk of contamination. Numerous low risk methods exist for introduction of sterile components to an aseptic isolator (e.g. pre-sterilized stoppers via autoclave bag with integral RTP, VHP airlock, depyrogenation tunnel, etc.) **Proposed Changes:** **[**465] “The required background environment for isolators can vary depending on the design of the isolator, its application and the methods used to achieve **disinfection**. The decision as to the supporting background environment should be documented in a risk assessment where additional risks are identified. Isolators with higher risk may require a cleaner background environment.”
475	**Comment:** We believe that all three are intended to be required, but at different intervals. **Comment:** We believe that all three are intended to be required, but at different intervals.

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: [474] "Integrity testing of the barrier systems and leak testing of the isolator and the glove system should be performed using **a combination of** visual, mechanical and physical methods. **Each method** should be performed at **unique** defined **intervals appropriate for that technique, developed using a risk based approach. At a minimum, integrity testing shall be undertaken** at the beginning and end of each batch **or campaign, a visual integrity check is required, as a minimum**, after any intervention that may affect the integrity of the unit."
476-477	This clause needs to allow for multiple lot campaigns without jeopardizing a production line with an intervention, (i.e. beginning and end of campaign should be good enough) **Proposed change:** At a minimum of the beginning and end of each batch and/or campaign
477-478	Following an intervention, in the middle of a batch, you don't want to use physical or mechanical methods and possibly compromise the manufacturing environment for that batch. Visual check, after interventions, should be enough and is currently industry practice **Proposed change:** …and following any intervention that may affect the integrity of the unit visual integrity checks should be performed.
497-499	"5.24 Clean rooms and clean air devices should be qualified in accordance with Annex 15 of EU GMP. Reference for the classification of the clean rooms and clean air devices can be found in the ISO 14644 series of standards." **Comment:** In ISO 14644, the filtering efficiency is based on MPPS. The definition of HEPA in "11. Glossary" is different from one in ISO 14644 & 29463. There is still no HEPA filter test interval specified **Proposed change (if any):** "and clean air devices" **should be deleted**. Proposed change (if any): WHO 4. 4.5 (every 6 months, but not exceeding 12 months) at least for grade A B
487-491	**Comment:** The term "Clean Air Devices" appears to refer to terminal filters (e.g. HEPA or ULPA) however, the phrase "Clean Areas" appears parenthetically after "clean air devices". The use of this term is unclear. **Proposed change:** Add "Clean Air Devices" to the Glossary. or replace with "terminal air filters".
505	**Comment:** Table 1 shows the at-rest value first. This has been a source of industry confusion with many companies citing this number as their primary design target. Furthermore, column 4 title does not match the order of the data below it (at-rest ISO class is listed first, but the column title indicates that in-operation would be first). **Proposed change:** Show the "in-operation" column first. This would align with the nomenclature in the fourth column and be less confusing overall.

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505-506	In the table, ISO classification in operation/at rest for grade D should be defined as '8[(a)]' To stay within the editorial foot note format, it is recommended to include a footnote citation with the last column '8[(a)]' **Proposed change:** 8[(a)]
510	**Comment:** ISO sample volume requirement are clear, the suggestion that "a higher sample volume" may be required is not helpful and will promote inconsistent classification studies. If no scientific basis for higher sample size is proposed, please delete this comment and rely on the ISO 14644 method for calculating sample size. **Proposed change:** [511] Delete "and sample volume"
510	This paragraph is very open to interpretation – can it be made more definitive?
522-524	**Comment:** This is an excellent upgrade to the definitions and is aligned with ISPE definition of "at-rest". However, the term "static" is not in the glossary. **Proposed change:** Add "static" to glossary as "at-rest" or "not operating".
529-531	**Comment:** Here batch data is allowed, this is in contrast to clause 5.28 where batch data is not allowed section 5.28 "Clean room qualification (including classification) should be clearly differentiated from operational process environmental monitoring **Proposed change:** In operation" classification, qualification and requalification may be performed during normal operations without nrisk for the product~~,~~ simulated operations or during aseptic process simulations (where worst case simulation is required).
533-535	**Comment:** The deletion of the recommended cleanup (recovery) time is not helpful. The 15-20 minutes period for Grade B was appropriate and easily achieved in a good design; the source of confusion was the lack of MOT for this test. We recommend referring to ISO 14644-3 recovery test as the MOT for recovery testing. The values in the table can serve as the limits. It should also be made clear that recovery testing is only required in Grade B and C spaces. **Proposed change:** "The particle limits given in Table 1 above for the "at rest" state should be achieved after a "clean up" period **of 15-20 minutes as demonstrated by recovery testing per ISO 14644-3**. The "clean up" period should be **tested** during the initial classification of the rooms.
540-549	**Table 2** **Comment:** The use of settle plates in grade B, C and D is not an efficient method because of the very low recovery (ref. Barbara M. Andon, Active Air vs. Passive Air (Settle Plate) Monitoring in Routine Environmental Monitoring Programs, PDA J Pharm Sci Technol November/December 2006 60:350-355l) The method should only be used where volumetric air sampling is not possible **Proposed change (if any):**

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	Table 2: Add in the foot notes: the use of settle plates in grade C/D area need to be assessed using a risk assessment considering the risk to the process
541 & 551	**Comment:** There appears to be a contradiction within this table and the foot note, …the recommended maximum limits for microbial contamination during qualification for each grade are given in Table 2… the table states that for Grade A areas the allowable Air sample (CFU/m^3) is 1. However, footnote (b) stat Proposed change (b) ~~It should be noted that for grade A the expected result should be 0 cfu recovered;~~ any recovery of 1 cfu or greater should result in an investigation. What is the rationale for changing from <1 to 1? **Proposed change:** Clarify intent
544	**Comment:** Change the title of Table 2 to "Recommended Maximum limits for microbial contamination in operation." There is contradiction of terminology in the document, sometimes use "level", sometimes "limit", There should be only one wording. **Proposed change (if any):** Would propose "level" across the document.
552-553	**Comment:** Clarification is requested on limits for qualification versus routine monitoring. Are these limits intended to be the same?
555-556+529	Many companies perform EMPQ during operations. **Proposed change:** 5.28 Clean room qualification (including classification) should be clearly **documented separately** from operational process environmental monitoring. **Classification should meet all requirements of ISO 14644-1**
558	**Comment:** "Periodically Qualification for clean room;" Are there any recommended qualification items for periodically qualification? Our understanding is "Periodically qualification items" are selected based on operation experience and risk assessment. **Proposed change (if any):** Provide guidance on minimum tests for periodic requalification
558-560	**Comment:** The re-qualification requirement intervals are close to FDA, but not quite there. For example, FDA specifies biannual requalification only for aseptic processing rooms. Suggestion: align with FDA for intervals. Further the specific requirements to formal re-qualification as opposed to the ongoing monitoring programs are not clearly specified. It should be specified that the section only applies to classification and "HVAC tests" **Proposed change (if any):**

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	Clean rooms should be ~~requalified~~ **classification should be verified and HEPA filters leak tested and velocity checked** periodically and after changes to equipment, facility or processes based on the principles of QRM **with supporting data**. **Airflow visualization should be performed in the area of any changes to equipment, facility or process, when the change is implemented**. For grade A ~~and B zones,~~ the maximum time interval for ~~requalification~~ **classification, leak testing and velocity testing of the HEPA filters** is 6 months. ~~For grades C and D, the maximum time interval for requalification is 12 months.~~
563-565	**Comment:** The language here is unclear, we believe the intent is to have limits that support product needs without causing undue risk to cleanliness. **Proposed change:** 5.30 Other characteristics, such as temperature and relative humidity, **should be controlled within ranges that align with product / processing requirements and support maintenance of** defined cleanliness standard**s**.
569-571	**Comment:** Soil on surfaces is a real challenge in some facilities, especially when returning to service. **Proposed change (if any):** …They should be cleaned and disinfected thoroughly in accordance with a written programme (for disinfection to be effective, cleaning to remove surface contamination **or disinfectant residues** must be performed ~~**first**~~ **regularly, based on QRM principles and data**).
571-573	**Comment:** It is suggested to clarify but also to allow the minimum regime of one disinfectant and one sporicide based on the following: • USP <1072> saying that resistance to antimicrobial agents (disinfectants) is less likely than resistance to e.g. antibiotics as the disinfectants are more powerful biocidal agents • The scheme of two disinfection agents has led to high residue levels on surfaces • A more superior disinfection scheme is one disinfection agent rotating with a sporicide • All rotation schemes must be based on classification, EM and/or risk assessment **Proposed change (if any):** …More than one type of ~~disinfecting~~ agent **to reduce the microbial level of surfaces** should be employed, and should include the periodic use of a sporicidal agent. **The rotation scheme must be based on classification, EM and/or risk assessment**
582-583	**Comment:** The language here is unclear, we believe the intent is to have solutions which are sterile filtered. Insisting on all sterile cleaning and disinfection agents raises the bar unnecessarily. **Proposed change:** Disinfectants and detergents used in grade A and B areas should be sterile **filtered during preparation**.
585-586	**Comment:** Even though we think it is not the intention, the text might be interpreted as the test of the disinfectants must be performed on the actual surfaces and equipment in the production facility. Therefore, we suggest specifying the intent further in the wording.

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: ~~Disinfectants should be shown to be effective when used on the specific facilities equipment and processes that they are used in~~ **The effectiveness of disinfectant and disinfectant processes used on the surfaces of the equipment and on the surfaces in the facilities should be demonstrated**
588 - 589	**Comment/rationale:** VHP/VPHP is a widely-used method for decontamination. No indication is provided here for validation (e.g. log reduction as per 8.46). Some generic sentence could be added to address validation. **Proposed change: (add txt)** 589 589 "… validation of fumigation or vapor phase disinfection method should be undertaken using QRM principles."

Equipment

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')*
593-595	Comment: User requirements and specifications are commonly used to establish intended use of equipment and link equipment design to the product and process. Proposed Change: 6.1 A written, detailed description of the equipment design should be produced (including user requirements/specifications, diagrams as appropriate) and kept up to date. It should describe the product and other critical gas and fluid pathways and controls in place.
597-598	Comment: it is not clear what time interval should be used for the review of alarm events. Qualification is used to verify alarms work as intended. Proposed change (if any): Change to "Equipment monitoring requirements should be verified during qualification. In Production operation, process alarm events should be reviewed and approved and evaluated for trends."
621	Comment: The requirement that all equipment (sterilizers, air handling and filtration systems, water treatment, generation, storage and distribution system) should be subject to qualification, should be aligned with quality risk management principles as described in Annex 15. Proposed change (if any): ~~All~~ Equipment such as sterilizers, air handling and filtration systems, water treatment, generation, storage and distribution system) should be subject to qualification, monitoring and planned maintenance; their release to Production operation use should be approved. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.
622	Comment:

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')*
	Typographical error for qualification Proposed change (if any): qualification
629-630	**Comment:** Use of separate, portable particle counters for qualification is unnecessary if permanent monitoring equipment is installed. The critical requirement is to minimize length and bends in sample tubing. **Proposed change:** 6.9 Particle counters should be qualified (including sampling tubing). ~~Portable particle counters with a short length of sample tubing should be used for qualification purposes~~. Add: Sample tubing length and number of bends should be minimized. Bend radii should be maximized.
633-635	Comment: Clarification is requested as to whether the assessment is intended to be performed before or after the maintenance. The wording "is to be" makes it sound like it has to be done prior to the work, which may not always be practical in many cases, especially in the case of an emergency. In this example, an assessment would be performed after the maintenance. Proposed change (if any): Where unplanned maintenance is performed on equipment critical to the sterility of the product, an assessment of the potential impact to the sterility of the product should be performed and recorded prior to returning the equipment to service.

Utilities

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')*
655-656	**Comment:** The typically defined critical parameters of a water system like conductivity, TOC content, endotoxin content, etc. are already subjected to regular trend analysis. Annex 1 is applicable above global GMP guide where trends analysis is described and requested in production data. **Proposed change (if any):** Suggest deleting line 655-656
658-660	**Comment:** It is important that the mentioned parameters are documented. However, these critical system attributes can be part of different documents. We would therefore recommend referring to documentation instead of drawing. In addition, the pipeline length is no critical system attribute since the turbulent flow is defined by Reynolds number. **Proposed change (if any):** "Current ~~drawings~~ documentation should be available that identifies critical system attributes such as: pipeline flow, pipeline slopes, pipeline diameter ~~and length~~, tanks, valves, filters, drains and sampling points"
662-663	**Comment:** Requirement for installing pipes and ducts and other utilities so they do not generate places difficult to clean,

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')*
	is not relevant to non-classified areas, which the current phrasing may be interpreted as intending. This shall be applicable to pipes and ducts installed in classified areas only for external surfaces. **Proposed change (if any):** "Installation of pipes and ducts and other utilities, located in clean rooms, should allow cleaning and disinfection of outer surface of the pipes."
672	**Comment:** As per current EP, "Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water". All major Pharmacopoeias (USP, JP, FB) as well consider Drinking Water Quality (pretreated as needed depending on final purification step to generate WFI) acceptable as feed water to generate WFI. As an example, Common industry practice both in EU Area and USA Area have thousands of applications of Distillation Processes by Vapour Compression Technology fed by Softened water quality and same number of application using Multi-effect Distillation where feed water is deionized quality but not Purified Water in terms of Chemical and microbiological limits. The comment is that the Annex 1 must be harmonized with EP monograph for WFI (0169) **Proposed change (if any):** "Water for injections (WFI) should be produced in accordance with current EP Monograph (0169), USP, WHO requirements., stored and distributed in a manner which prevents microbial growth, for example by constant turbulent circulation preferably at a temperature above 70º C. If distribution networks or sub-loops are operated cold, a daily sanitisation at a temperature above 70º C for validated duration is required. Where the WFI…"
672-676	**Comment:** As the new annex also includes the intent of WFI production via RO, the section should be reviewed to ensure the consistency and intent with this alternative production method, for example as per the recent document "Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies" **Proposed change (if any):** Where the WFI is produced by methods other than distillation, further techniques post Reverse osmosis (RO) membrane such as Electro De-Ionization (EDI), or additional membrane (nanofiltration or ultra-filtration) should be considered.
674-676	**Comment:** It is not clear whether "purified water" as it is used in this section is intended to refer to water that has been pre-treated or Purified Water as described in the relevant Pharmacopeia. **Proposed Change:** Introduce "Purified Water" definition in Glossary: "Purified water is obtained by distillation, ion exchange, reverse osmosis or other appropriate processes from drinking water"
677-679	**Comment:** Water systems should be validated to maintain the appropriate levels of physical, chemical and microbial control, taking seasonal variation into account

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): "Water systems has to be validated following risk base assessment taking into account seasonal variations."
681	**Proposed change (if any):** Suggest incorporating in Glossary "Turbulent regime" definition. "Water flow, in distribution systems, should remain turbulent through the pipes to minimize microbial adhesion."
683-684	**Comment:** Sloping and draining are not possible in all occasions, e.g. for membrane (RO) water production systems. It should therefore be optional to perform a conservation instead of drainage, via addition of chemicals, for relevant water production system, e.g. for RO. **Proposed change (if any):** [684]...complete drainage for storage tank and distribution vessel…
688-689	**Comment:** Bulk WFI pharmacopoeia is not considered as sterile. We suggest rewriting this section. **Proposed change:** Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should be periodically sanitised, and the integrity of the filter tested before and after ~~use~~ replacement. Appropriate control methods should be applied to minimize the potential introduction of contaminants when vent filters are changed.
691-696	**Comment:** It is not necessarily possible to "prevent" the formation of biofilms. Each of the techniques described in this section describes a way to treat biofilms when they occur. Additionally, heat is very effective at killing biofilms, but sterilization is not required. Hot water sanitization above 65C is effective to kill biofilms. More extreme actions such as sterilization or chemical disinfection should only be taken for cause if indicated by routine monitoring data and not on a routine schedule. Definitions of sanitization and disinfection should be included in the glossary. This section also mixes techniques that might be used for generation equipment, such as regeneration, with techniques that are more applicable to distribution systems. Additionally, the terms alert and action *limits* are used in this section, but the terms alert and action *levels* are defined in the glossary **Proposed Change:** 7.13 Periodic sanitization (thermal or chemical) of water systems should be carried out to mitigate the formation of biofilms if the system is not kept in a continuously sanitizing condition (temperature greater than 70 C). Other actions, such as disinfection of distribution piping or regeneration of generation steps, may also be used in response to adverse trends in the routine monitoring data. The use of chemicals for this purpose should be followed by sampling or the use of online monitoring to ensure their removal before the start of use of the water system. ~~To prevent the formation of biofilms, sterilization or disinfection or regeneration of water systems should be carried out according to a predetermined schedule and also when microbial counts exceed action and alert limits. Disinfection of a water system with chemicals should be followed by a validated rinsing procedure. Water should be analysed after disinfection/regeneration; results should be approved before the start of use of the water system.~~
701-708	**Comment:** Please update the use of "outlets" in favour of "points of use" as water systems typically have quite a number of other "outlets" in technical areas that are used for complete system drainage or other non-processing reasons, and these "outlets" do not typically require sampling. Industry experience also indicates that

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')*
	inspectors frequently interpret examples, such as the one offered about the worst-case sample point being located at the end of the distribution loop, as absolute requirements. A complex point of use will often be a worse condition than the loop return in the case of microbiological contaminants, which are unlikely to be uniformly distributed. Clarification or rewording should also be provided about the intent of sampling this worst-case point "each time the water is used" – is this intended to mean on the day of use? Additionally, the terms alert and action *limits* are used in this section, but the terms alert and action l*evels* are defined in the glossary. The requirements for breach of an action limit/level in this section are different than those imposed by the definition in lines 2023-2024. Alert levels may be calculated based on the qualification, but may also be calculated based on more recent ongoing monitoring data. Please also define manufacturing processes if this phrase remains in the final text. Interpretation is understood as uses of the water not directly involved in the formulation, such as cleaning, but clarity could be improved on this point **Proposed Change:** "Regular ongoing chemical and microbial monitoring of water systems should be performed with alert levels based on the qualification or a review of ongoing monitoring data that will identify an adverse trend in system performance. Sampling should include all points of use at a specified interval. Risk assessments should be used to determine potential worst case sampling locations and an appropriate sampling frequency." Breach of alert or action levels should be handled according to the alert and action level definitions in the glossary. We suggest incorporating in Alert level actions (glossary) required when breach is made
704-706	**Comment:** The text "*each time the water is used for manufacturing and manufacturing processes*" shall can be misinterpreted as being once per batch/campaign all the way to every time water is filled into the process (~multiple times a day/hour). Text to be re-considered how frequent a specific user-point shall be sampled depending on when manufacturing and manufacturing processes take place – e.g. sampling the same day as manufacturing and manufacturing processes occurs. **Proposed change (if any):** "A sample […] should be included each time the water is used for manufacturing, **e.g. each production day**, …."
710-711	**Comment:** Suggested change of wordings in line 710 to 711 and addition of a sentence to clarify the intent **Proposed changes (if any):** "WFI distribution systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity. WFI generation systems should include continuous monitoring of conductivity. Implementation of TOC monitoring should be based on QRM principles."
715	**Comment:** The same comment provided to WFI Generation is applicable to Pure Steam Generation, which ultimately if associated with a condensation step become a Single Effect Still Generation process for WFI production. Pure Steam, when condensed, become WFI. The only written Pharmacopoeia monograph about Pure Steam is the USP. The text is: "Pure Steam is water that has been heated above 100° and vaporized in a manner that prevents source water entrainment. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations, or with drinking water regulations of the European Union or Japan, or

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')*
	with WHO drinking water guidelines. It contains no added substance. The level of steam saturation or dryness, and the amount of no condensable gases are to be determined by the Pure Steam application" Therefore, the feed-water for Pure Steam Generators should be either drinking water or Purified Water. No need of low level of endotoxins because the Pure Steam Generator must be designed in order to prevent source water entrainment and provide the same Log reduction effect same as WFI Still which is, as said above, a Pure Steam Generator plus a condensing Unit **Proposed change (if any):** Pure Steam generator should have as feed water either Drinking or Purified water, as required by WFI Monograph for WFI Production Process. Feed water should contain no added substance. Pure Steam Generators must be designed to prevent source water entrainment in order to provide an appropriate level of endotoxin reduction to meet the quality limits of WFI, where Steam come into contact with material, equipment or components which ultimately come into contact with parenteral products.
718	**Comment:** Steam used for sterilization ought to be Pure Steam. Pure steam may not contain any additives at all. **Proposed change (if any):** "Steam used for sterilization processes should be compliant with Pharmacopoeia such that its condensate meets the specifications of WFI."
727-733	**Comment:** The statement that compressed gases must be free from oil cannot be verified with currently available sampling technology – the limit of detection is not zero. A statement that oil free compressors should be used is more appropriate, and the statement already requires alignment with the appropriate monograph if appropriate, which leads to an oil specification that is not zero (such as the monograph for medicinal air). Additional clarification about where sterilizing filters must be used and when those filters should be integrity tested is also necessary. It is not necessary to place these filters at the point of use (they can be used to filter several use points in an area) unless the filters also provide part of the sterile boundary for a process. There are also statements in sections 8.85 and 8.86 related to gas filtration that are redundant with this section or would be better placed in this section. **Proposed Change:** "Compressed gases that come in direct contact with the product/container primary surfaces should be of appropriate chemical, particulate and microbiological purity, compressed without the use of oil and ~~free from oil~~ with the correct dew point specification and, where applicable, comply with appropriate pharmacopoeial monographs. Compressed gases must be filtered through a sterilizing filter (with a nominal pore size of a maximum of 0.22µm) ~~at the point of use.~~ The avoidance of unintended moistening or wetting of the filter is important and can be achieved by the use of hydrophobic filters. Where these filters are used as part of the sterile boundary, ~~used for aseptic manufacturing,~~ confirmation of the integrity of the final sterilization gas filter should be considered as part of the batch release process."
740-743	**Comment:** Clarify the requirement is only for aseptic areas. It is not for all filling rooms. **Proposed change (if any):**

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')*
	"Major items of equipment associated with hydraulic and cooling systems should, where possible, be located outside the aseptic room. Where they are located inside the aseptic room there should be appropriate controls to contain any spillage and/or cross contamination associated with the hydraulics of cooling system fluids."
745-746	**Comment:** Clarification is requested if the term 'any leaks' 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). **Proposed change (if any):** "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."
748-749	**Comment:** Generalize the requirement to allow for appropriate measures **Proposed change (if any):** "The cooling circuit should be subject to periodic control and following any maintenance."
751	**Comment:** "There should be periodic cleaning/disinfection of both the vacuum system and cooling systems" **Proposed change (if any):** Not exactly sure how this is feasible. The cooling system they are referring to a chilled water system? Not feasible to clean/disinfect. Not sure what this is getting at. Please clarify or delete altogether.
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)."

Production and specific technologies

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
799	ISPE comment Clarification required; "Precautions to minimize … pyrogen" Does this mean only endotoxins? To be incorporated in glossary
792-799	Comment:

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	This content is repeated earlier in the draft; materials liable to generate fibers is not good terminology as flexible materials are liable to generate fibers – the materials selected are based on the best available technology that will meet the requirements.
805-807	Original text: 805 8.9 Where possible, the use of equipment such as RABS, isolators or closed systems, should 806 be considered in order to reduce the need for interventions into the grade A environment and 807 minimize the risk of contamination. Automation of processes should also be considered to Comment/rationale: This kind of formulation as exposed is probably too light "where possible...should be considered", giving basically wide option to not implement these technologies while they effectively reduce contamination risks. different wording is proposed to emphasize the importance of a serious assessment on feasibility of RABS or Isolator adoption in aseptic processing Proposed change: 805 8.9 Where possible, the use of equipment such as RABS, isolators or closed systems, must ~~should~~ 806 be considered in order to reduce the risk of contamination caused by interventions into the grade A. Automation of processes should also be considered to
807-809	Comment Please clarify if automation of processes must be considered as the first option and all the others just if it is not feasible or it is just one of the options to choose and to be supported by a RA as the others. Proposed change: Based on risk analysis new technologies should be preferred where suitable.
811 and 814	Comment: To avoid confusion the document should be specific that this requirement applies to aseptic operations. Because if it is not specific then in table 4 grade A "Removal and cooling of items from heat sterilizers" could be interpreted as also applying to terminally sterilized closed containers of product. Proposed change (if any): Examples of aseptic preparation operations to be carried out ….
814 Table 4	Comment/rationale: We suggest specifying that grade A is to be used for: the removal and cooling of not wrapped /sealed items from heat sterilizers and grade B or C for transport and preparation of packaged wrapped /sealed equipment, components and ancillary items for introduction into the grade A zone.
814 Table 4	Comment: Transfer of open/partially stoppered vials under grade A supply (8.14)? is grade B required for removal of sealed product – previously it could be done in CNC, why the change? (see also 8.17). Proposed change Include in the table 4 a section with activities where grade A air supply is required.
815	814 Table 4: Examples of operations and which grades they should be performed in 815 A Critical processing zone.

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Aseptic assembly of filling equipment. Aseptic connections (should be sterilized by steam-in-place whenever feasible). Aseptic compounding and mixing. Replenishment of sterile product, containers and closures. Removal and cooling of items from heat sterilizers.for unwrapped materials Staging and conveying of sterile primary packaging components. Aseptic filling, sealing, transfer of open or partially stoppered vials, including interventions. Loading of a lyophilizer Grade A air supply unloading of a lyophilizer with non-capped vials Table 4: Unclear or incorrect statements e.g.: “Removal and cooling of items from heat sterilizers in Grade A”– this is not necessary if the goods are sealed “Aseptic connections” – pre-sterilized single use connectors are not steamed-in-place “Staging and conveying of sterile primary packaging components” - Not necessary if the goods are sealed “Removal and cooling of items from heat sterilizers must be under grade A conditions unless the items are adequately protected against contamination”
821 - 823	The text is not clear, suggest edits to clarify the expectations considering potential changes in the requirements; Proposed change: (add txt) 821 Where the product is not subsequently sterile filtered, the preparation of equipment, 822 components, ancillary items and products should be done in a grade A environment with 823 at least a grade B background. Where an isolator or RABS is used the background should be justified (typically grade D).
840 - 841	Comment: The request instead of Laminar flow is to use Unidirectional Laminar Flow. Proposed change: “The transfer of partially closed containers to a lyophilizer, should be done under grade A conditions (e.g. HEPA filtered positive pressure) at all times and, where possible, without operator intervention. Portable transfer systems (e.g. transfer carts, portable Laminar Unidirectional Flow Work Stations, etc.) should ensure that the integrity of the environment is maintained during the transfer
845	Add a definition for non-intrinsic aseptic connections to the glossary
847-848	The requirement is for the items to be sterilized, this should allow for gamma and other sterilization methods as well Proposed change: Whenever feasible, product contact piping and equipment should be pre-assembled, then cleaned and sterilized in place, unless other means of maintaining sterility such as the use of pre-sterilized single use transfer systems or aseptic assembly of pre-sterilized equipment which cannot be sterilized in place
855-856	Comment: Comment to the text “The duration for each aspect of the aseptic manufacturing process should be limited to a defined and validated maximum, including: - a. Time between equipment, component, and container cleaning, drying and sterilization. - b. Holding time for sterilized equipment, components, and containers prior to and during filling/assembly.”

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	In regard to the time duration: Validation is not always required. If equipment has a low bioburden after cleaning and is stored dry and protected from external contamination then the equipment is not subject to clean hold time validation (See PDA Technical Report 29 p. 78, ref. 4) "If stored in a dry state and if protected from external contamination (e.g., by sealing the equipment or by covering any openings with appropriate "GMP" covers), formal studies to demonstrate lack of microbial proliferation may not be necessary." In regard to the holding time; Validation is not always required. E.G. sterile and pressurised equipment is subject to risk assessment and not included in sterile hold time validations if a leak test is performed routinely (see VALIDATION OF ASEPTIC PROCESSES, PIC/S, PI 007-6, 1st January 2011, ref. 5) Proposed change (if any): "The duration for each aspect of the aseptic manufacturing process should be limited to a defined and validated maximum, including: - a. The requirement for validation of time between equipment, component, and container cleaning, drying and sterilization, should be based upon a risk assessment. - b. The requirement for validation of holding time for sterilized equipment, components, and containers prior to and during filling/assembly should be based upon a risk assessment."
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.
877-878	Clarification of the scope is required suggest text change to; …Partially stoppered vials or partially stoppered prefilled syringes should
879	Comment: The term LAF should be added to the glossary. In addition, laminar flow is not likely, suggest using the term unidirectional. Proposed change (if any): segregation from operators) or grade A unidirectional carts (with suitable grade B background) …
883-890	8.18 ---------- 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. It should be noted that visual inspection alone is not considered as an acceptable integrity test method. Comment: ✓ There is no method to check the integrity directly in manufacturing. To verify the sterility integrity, the detector which could detect the leak velocity less than 10-5 Sccs would be needed. However, there is no such detector currently available, so to detect the seal pressure of rubber stoppering pressure and visual inspection of aluminum cap formed shapes 100% inspection is required – also QRM and statistical methods are two possible approached –

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	the statistical method is preferred… Proposed change (if any): A statistical plan should be used to define the sampling of containers closed by other methods the integrity test method should be validated. It should be noted that visual inspection alone is not considered to be an acceptable integrity test method
883-890	Comments New technologies avoiding stopper removal during filling could be considered. Proposed change [886] Closed containers filled through a self-reclosing membrane that is further resealed, should not be 100% tested for closure integrity provided the sealing process is validated and subject to 100% parametric release and based on risk assessment
892-893	Comment: The definition of “Containers sealed under vacuum” is not clear. What is meant by “vacuum”? Most containers containing freeze dried product are sealed at pressure below atmospheric (e.g. 0,9bara) and there are no requirements for measuring the pressure. However, the Headspace content should be evaluated during time. For products sealed under complete vacuum (e.g. <0.01bara), it is necessary to verify that the pressure is maintained. We therefore suggest the requirement changed, partly according to USP <1207> (ref. 6). 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. For products that demand package headspace content preservation or sealed under vacuum, it is appropriate that the integrity test for stability studies verify the continued presence of specific headspace gases or sub atmospheric pressure over time.”
899	Change to Crimping of vial / cartridge caps should be located at a station equipped with adequate air return and physical separation from the filling process.
902 - 906	Comment: If vials capping is undertaken outside the aseptic core, what should be the surrounding environment of the grade A protection be? Proposed change (if any): if vials are capped outside the aseptic core “critical area”, vials should be protected by grade A air supply with a minimum background of controlled non-classified
910	Appropriately qualified methods for stopper height detection should be in place, with stoppers outside the specification rejected prior to capping.

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
915	Suggest revising text to: capping station, appropriate measures should be used to minimize microbial contamination.
919	Suggest revising text to: minimizing the risk of microbial contamination of the capping operation.
922-924	8.26 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. QRM principles should be used for determination of defect classification and criticality. Comment: QRM principles is not clear in this requirements in this paragraph. Proposed change (if any): 8.26 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. QRM principles should be used to determine the defect classification and criticality considering the potential risk to the patient.
931-932	Comment: To sentence “Critical defects should not be identified during any subsequent sampling of acceptable containers as it indicates a failure of the original inspection process” It is unclear if the sentence above refers to: 1. No critical defects must be found during sampling after inspection, independent of the sampling size, and thereby only sampling plans with acceptance number 0 is accepted? Or 2. Critical attributes only should be tested at one stage in the process? Comment to point 1: It can be concluded that according to ISO 2859-1 and ISO 2859-2 it is allowed to have critical defects in a batch after the original inspection process: When using AQL sampling plans for inspection of continuous batches, a sample is taking in accordance with ISO 2859-1 and it is evaluated if the quality level (percent non-conforming items) of the batch is acceptable. If AQL is 0.1% the sampling plan according to ISO 2859-1 e.g. is (800,1) for Code Letter P, general inspection level II, Tightened inspection. Thereby the sample size is 800 and if ≤ 1 non-conforming item is identified; the batch is accepted. As 1 non-conforming item is accepted according to the AQL sampling plan, it can be concluded that critical defects is allowed in the batch after inspection. Therefore, it should also be allowed to identify critical defects during subsequent sampling of a batch, without suspecting a failure in the original inspection process. Moreover, if ISO 2859-2 is used for inspection of an isolated batch, the sampling plans for batch sizes > 35000 all have sampling plans with acceptance numbers > 0. Comment to point 2: If the sentence above refers to point 2, we understand it as if inspection for a critical defect is done during e.g. filling, inspection for the same type of defect should not be made during e.g. assembly.

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	In either case, the sentence is not clear so we propose it is deleted. Proposed change (if any): Delete the sentence "Critical defects should not be identified during any subsequent sampling of acceptable containers as it indicates a failure of the original inspection process"
935-936	Comment: As a person is normally not validated but qualified we suggest changing validated to qualified Proposed change (if any): "Inspection rates should be appropriately ~~validated~~ qualified."
938-939	Comment: annual eye examination as stated is too general and can be mis-interpreted. Proposed changes: Annual eye examination program for visual inspection operator qualification must be adequatly justified.
948-949	Comment: These two sentences: "Results of the inspection should be recorded and defect types and levels trended." And "Reject rates for the various defect types should also be trended." Both ask for trending of the reject rates under the assumption that "level" and "rate" here have the same meaning. And if this is not the intention, then further clarification is needed. Propose change (if any): "Results of the inspection should be recorded and defect types and levels trended. ~~Reject rates…..~~
956	Comment: 8.30 Where possible, finished product should be terminally sterilized using a validated and controlled sterilization process as this provides a greater assurance of sterility than a validated and controlled sterilizing filtration process and/or aseptic processing. Proposed change (if any): Where possible, finished product should be terminally sterilized using a validated and controlled ~~sterilization process as this provides a greater assurance of sterility than~~ aseptic processing.
958	Add to general comments
958	Grammar – the use of "a" in "a" sterilization is not required [958] to undergo ~~a~~ sterilisation
982	Clarify the requirement; "with a maximum interval of a year".
1007	Comment: Labelling of each basket, tray etc. should be labelled as described in the sentence "Each basket, tray or other carrier of products, items of equipment or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilized"

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	But requiring the information should include “the material” name is an unnecessarily requirement as long as there is a unique identification. Proposed change (if any): “Each basket, tray or other carrier of products, items of equipment or components should be clearly labelled with the material name, its batch number and unique identification together with an indication of whether or not it has been sterilized”
1022	Comment: The sentence: “Where protection is achieved by containment in sealed packaging this process should be undertaken prior to sterilisation.”- raise a concern as some equipment, designed for washing, sterilisation and aseptic processing of pharmaceutical closures (eg. Rubber stoppers, rubber pistons) will aseptically pack the items in protective materials after ended sterilisation, it is recommended to open up for this possibility also. Proposed change: “Where protection is achieved by containment in sealed packaging this process should be undertaken prior to sterilisation or by aseptic transfer of the items to the protective packaging after sterilization”
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 risk analysis to define the monitoring points.
1091	…this time must be determined for the items that form the load to be processed e.g. solid parts (e.g. tweezers), long hollow parts (e.g. tubes), containers (e.g. bottles buckets, beakers) to ensure identification of the worst case.
1114-1119	Comments: Validation should include a consideration of equilibration time…revalidation should be performed annually… Proposed change: Requirements listed in EN 285 for technical specifics with validation requirements
1121-1124	8.58 ---------- The frequency of testing should be based on the principles of QRM. Comment: In this paragraph, the term “QRM principles” is inadequate. Proposed change: The frequency and acceptance criteria for testing should be through assessing the risk of microbial contamination.
1152	Comment: “Once a system has been sterilized by SIP it should remain integral prior to use, the maximum duration of the hold time should be qualified.”

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	In agreement with comments given for chapter 8.16/Line 855-856 we propose the following: Proposed change: Once a system has been sterilized by SIP it should remain integral prior to use.
1140-1143	Older autoclaves may not always allow SIP of vent filter Proposed change …Care should be taken to ensure that materials or equipment are not contaminated…into the chamber during these phases… Exceptions to the use of a steam in place system for the air filter must be assessed and justified based on a risk assessment.
1145-1153	…Where Sterilization in place (SIP) systems are used…the maximum hold time should be qualified… For Systems with a qualified quantitative test method for integrity at the timepoint of use or a qualified and alarmed continuous monitoring system for the protective conditions the maximum specific holding time can be determined using a risk assessment.
1151	The use of the term routine validation is confusing here, continuous monitoring is typically used in lieu of revalidation
1162-1165	Comment: Airflow patterns in tunnels are not relevant due to the narrow geometry and the short distance between supply and return air, as long as the pressure regimen protects the cleaner zones. Proposed change: [1162] Tunnels should be configured to ensure that the ~~patterns~~ airflow protects the integrity and performance of the [1164] sterilizing zone, by maintaining a stable pressure differential ~~and airflow pattern~~ through the tunnel from the higher grade area to the lower grade area.
1166-1168	Comment: The use of the wording: '*periodic test should be performed to demonstrate filter integrity*' suggests that HEPA integrity tests which are used in room systems (i.e. using volatile organic compounds) be used for dry heat ovens. These may present a fire hazard and potential product contamination. The proposed wording allows for the use of a suitable test method. Proposed change (if any): All air supplied to the tunnel should pass through a HEPA filter; periodic tests should be performed to demonstrate filter integrity performance is maintained.
1167-1169	Comment: This could be interpreted as a requirement to have depyrogenation tunnel which have a sterilizable cooling zone as a feature. Although this is already common industry practice at least for isolator filling lines. Proposed change (if any): Any tunnel parts that come into direct contact with sterilized components should be appropriately sterilized or disinfected.
1208	Comment: The ISO standard is provided as an additional reference.

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change (if any): Guidance regarding ionising radiation sterilization can be found within Annex 12 of the EU GMP and in ISO (11137).
1214 - 1215	Comment: The document would be clearer if there was rationale either when sterilization by radiation is acceptable or including the rationale why it is generally unacceptable. Proposed change (if any):
1236-1238	Comment: The ISO standard is provided as a reference. Need to check for this section if parametric release is acceptable for sterilisation by Ethylene Oxyde linked with EU GMP parametric release annex. Proposed change (if any): Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load unless parametric release (as per ISO 11135) has been authorized by the National Competent Authority.
1258-1261	Comment: It is unclear what the additional risks are for a validated filtration process.
1267	Comment: The filter characteristics should not be adversely affected by the product to be filtered. The filter should be compatible and not dissolve in the fluid. The BP may change (filter characteristic) and not be recoverable due to adsorption of surfactants to the membrane but the filter can still produce sterile filtrates (not be adversely affected). Proposed change (if any): Similarly, the filter should be compatible with the fluid and not be adversely affected by the product to be filtered.
1287-1289	Comment: Implementing an in-line filter test may add additional aseptic steps and add additional sterility assurance risks to the aseptic process. The risks and benefits for each filtration design should be evaluated. Note, triple filtered aqueous products have a different risk as compared to double filtered high viscous and concentrated product. Proposed change (if any): f) Permit in-place integrity testing, preferably as a closed system, prior to filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product. It is recognized that for some product and filter combinations, this may not be possible or may add additional risk. In these cases, an alternative approach may be taken as long as a formal risk assessment has been performed evaluating the risk of additional aseptic steps and the risk of a non-integral filter not being detected.
1301-1302	Comment: For a fixed volume of fluid being filtered through a known filter, only two of the three following parameters is needed to ensure the filtration process is in control: filtration time, pressure across the filter, and flow rate. This is the reason for recommending the word change from should to may. Proposed change (if any):

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Filtration parameters that should be considered in validation and routine processing may include but are not limited to:
1307	Comment: Grammar correction Proposed change (if any): The wetting fluid used for the filter integrity testing should be based on the filter manufacturer's recommendation or the fluid to be filtered.
1331-1334	Comment: The term "on line" is not defined and has a high risk of being misinterpreted. It is critical that the filter membrane cartridge remains seated in its housing or capsule, but it is not necessary for the entire filter assembly (combined membrane and capsule / housing unit) to remain connected to the fluid flow path after conclusion of filtration. This could be an interpretation of term "on line" and would be a significant departure from common industry practice where the entire filter assembly is often moved for integrity testing. Note: performing on-line testing may require connecting a filter test device to the liquid path directly in the Grade A environment, since this test equipment cannot be sterilized, which can result in increased risk to product sterility. 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 testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test. The sterilizing membrane must remain seated in its housing or capsule for integrity testing.
1334-1336	Comment: Performing integrity testing post sterilization and pre-use can add complexity to the design of the filtration system which can result in increased risk to product sterility. Examples include but are not limited to (a) designs with two filters in series and (b) single use systems (SUS) which would require an increased number of manual operations prior to actual use of the filter for product. For gamma sterilized SUS, the risk of affecting the filter membrane during the sterilization is almost non-existent based on validation data, assuming the filter is composed of gamma compatible materials. Based on the presented risk, it is recommended a risk-based approach to pre-use, post-sterilization integrity testing be allowed. The risk of "defect-masking," and thus the need for this pre-use testing, can be eliminated for some filtration processes. Proposed change (if any): It is recognised that for some filtration processes, the post sterilization, pre-use test may not be possible or may add additional risk (e.g. closed SUS, small batch sizes); in these cases, an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved.
1346-1347	Comment: Hydrophobic filters will not prevent unintended moisten of the filter or filter equipment. Moistening is usually caused by condensation and gas moisture droplets. A hydrophobic filter is required to avoid permeation of the filter with moisture and hence the grow through of bacteria. Proposed change (if any):

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	For gas filtration, the avoidance of unintended moistening ~~or wetting~~ of the filter and hence bacterial grow through should be prevented. This can be achieved by the use of hydrophobic filters.
1349-1352	Comment: There is less risk to the sterility of the product to validate onsite that the sterilization process does not harm the filters, than to try to integrity test 2 filters in series pre-use, post sterilization. Proposed change (if any): Where serial filtration (one filtration is followed by a subsequent 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 to detect any damage during processing.
1356-1358	Comment: Correcting grammar Proposed change (if any): Bioburden samples should be taken prior to the first filter and the sterilizing filter. Systems for taking samples should be designed so as not to introduce contamination.
1366 - 1373	Comment To make the difference between open containers that are closed by fusion, and containers that are already mechanically closed before being secured by fusion (as AT-Closed Vials for instance) Proposed change [1372] continuous process. All such containers are considered to be closed by sealing by fusion and, as such, fall under the 100% integrity testing
1419-1420	Comment: Correcting punctuation Proposed change (if any): It is not normally possible to perform environmental monitoring within the parison during 'operation'. Monitoring of the background environment…
1423-1425	Comment: Improved wording Proposed change (if any): The environmental control and monitoring program should take into consideration the complex airflow paths generated by the BFS process and the effect of the high heat outputs of the process.
1460-1461	Comment: With appropriate risk analysis and identification of potentially associated lots in the case of a sterility assurance concern with the lyophilizer, sterilization between each load in a campaign of the same product may not be necessary. Recommend incorporating wording from ISO 13408 – 3, Aseptic processing of health care products (Part 3:

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	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.
1478-1479	Comment: The conveyor system may not provide a Grade A environment. There are confusions between loading and unloading lyophilisers. Proposed changed: In table 4 remove unloading of lyophiliser in Grade A it can be done under Grade A air supply. [1478] clarify transport (conveyor, cart…)
1488-1490	Comment Belt systems are not considered 'utensils'. Note, belt systems used for automatic loading/unloading are sanitized, not sterilized. Proposed change (if any): Clarification is required as above
1512-1515	Comment: The paragraph suggests that a grade D is always required at minimum. But such containers are even shipped globally without any classified area, just in their closed system. Proposed change (if any): The background in which closed systems are located will vary. If there is a high risk that the system will not remain integral during processing it should be located in a grade A environment. If the system can be shown to remain integral at every usage then lower grades, including grade D, can be considered. For transport and shipping of closed systems outside classified areas, specific conditions (multibagging and packaging integrity checking) should be determined and specified based on QRM.
1519-1522	Comment: The wording 'designed to replace reusable equipment' implies that SUS is only deployed in retrofitting situations. Proposed change (if any): Single use systems (SUS) are used in manufacture of sterile medicinal products as an alternative to reusable equipment. SUS include individual components, and combinations of components such as bags, filters, tubing, connectors, storage bottles and sensors.
1527-1528	Comment: The document states 'Interaction between the product and product contact surface (adsorption, leachable and extractable).' These interactions apply equally to non-disposable equipment.
1532	Comment: The document states 'Increase in number and complexity of manual operations and connections made.' Note: A good design can simplify operations for the end user.
1536	Comment:

Line number(s) of the relevant text	Comment and rationale; proposed changes 1. *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	The risks of performing pre-use integrity testing for sterilizing grade filters applies to both SUS and stainless steel systems.
1538	Comment: The risks of performing integrity testing applies to both SUS and stainless steel systems.
1540	Comment: Stainless steel systems can develop pin holes and have leaks issues too.
1550-1552	Comment: Compatibility of materials typically refers to if the fluid dissolves or degrades the materials of construction. I think what you are trying to determine is if the SUS hurts the product. Proposed Change (if any): The adsorption and reactivity of the product with the product contact surfaces should be evaluated under the process conditions.
1574-1575	Proposed change (if any): Prior to use, each piece of SUS should be at least visually checked to ensure that they have been manufactured and delivered in accordance with the approved specification.

Viable and non-viable environmental and process monitoring

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')*
1611 - 1614	**Comment:** The addition of QRM requirements ties to the rest of the documents expectations for risk control, and defining that trend analysis is a requirement is made early on in this chapter. **Proposed change (if any):** Routine monitoring for clean rooms, clean air devices and personnel should be performed “in operation” throughout all critical stages, including equipment set up. The locations, frequency, volume and duration of monitoring should be determined based on the risk assessment and the results obtained during the qualification. The monitoring of these areas should be performed in accordance with the principle of QRM and provide sufficient data to allow effective trend analysis.
1625 - 1627	**Comment:** The choice of "limits" vs "levels" is an overall document choice - but should be consistent. "Appropriate" requires that data be analysed for any trend variance. Levels are determined by a high threshold value based upon data from a process, and limits are those prescribed by Pharmacopoeia or regulatory documents standards. In this section that the levels are set by trend analysis and so are site dependant and not pharmacopoeia neither regulatory documents.

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): [1625] Appropriate alert and action levels should be set for the results of particulate and microbiological monitoring. Alert limits should be established based on results of Performance Qualification (PQ) tests or trend data and should be subject to periodic review
1629	**Comment:** The ≥ 0.5µm limit remains and should be set appropriately (see 9.8). **Proposed change (if any):** Change of c to C (typo) The alert levels for grade B, C and D should be set based on the area performance, with the aim to have levels lower than those specified as action levels, in order to minimise risks associated and identify potential changes that may be detrimental to the process.
1653	**Comment:** The table and text nomenclature for ≥ 0.5µm and ≥ 5.0µm, should be used as standard throughout. Standardization is required. **Proposed change (if any):** ≥ 5.0 µm
1653	**Comment:** There is no rationale for using a value of 20, especially as now 1m^3 sample volume is not required. The alarm limit for the ≥ 5.0µm particle concentration should be defined by trend analysis - see note 2. **Proposed change (if any):** Remove the limit of 20 particles.
1667 - 1669	**Comment:** The instrument flow rate is not sample volume, changed for clarification. The sample volume argument becomes moot with the change from specified limits to meet room classification at ≥ 5.0µm particle concentrations. **Proposed change (if any):**

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')*
	The grade A zone should be monitored continuously and with a suitable sample flowrate (at least 28 litres per minute; 1 cubic foot per minute) so that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert or action limits are exceeded.
1671 - 1676	**Comment:** Clarity to require a risk assessment for the Grade B areas, and not just similar to Grade A. There are areas in a Grade B environment which would not require system based monitoring but routine using a portable instrument. **Proposed change (if any):** ~~It is recommended that a similar system be used for grade B zones although the sample frequency may be decreased. The design of the monitoring system should be based on risk assessment and be commensurate with the risk of the process to the product sterility assurance. The grade B zone should be monitored at such a frequency and with suitable sample sizes that the programme captures any change in levels of contamination and system deterioration. If alert limits are exceeded, alarms should be triggered.~~ For grade B, the environmental monitoring system should be based on risk assessment and be commensurate with the risk of the process to the product sterility assurance. The grade B zone should be monitored at such a frequency and with suitable sample sizes that the programme captures any change in levels of contamination and system deterioration. If alert or action limits are exceeded, alarms should be triggered.
1703 - 1705	**Comment:** Clarity of language, as 'measuring' ≥ 5.0µm particles is performed not 'monitoring' for room classification. There was discussion around whether or not the ≥ 5.0µm should be included in room monitoring at all, and although for room classification the number of expected ≥ 5.0µm particles is so low that statistically the mathematics involved in proving compliance is unsuitable, the monitoring over time of ≥ 5.0µm activity still demonstrates differentiation of possible contamination events. There are studies which demonstrate the mean size of free floating viable organisms exist above the ≥ 5.0µm size range, this monitoring allows for differentiation of those particular contaminating events. There are occasions where ≥ 5.0µm particles may be generated at a rate greater than that of ≥ 0.5µm particles and in these instances an investigation should be established. Until Alternative Microbial Methods are established and an acceptable practice, this differentiated data proves useful. So long as the values are determined by risk and such events do not necessarily require batch failure but process review. **Proposed change (if any):** [1703] Although measuring ≥ 5.0µm particles is not required for room ~~qualification and~~ classification purposes, it is required for routine monitoring purposes as is an important diagnostic tool for early detection of machine, equipment and HVAC failure.
1714 - 1716	**Comment:** The requirement to review trended data based on site conditions should be performed.

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): Monitoring conditions such as frequency, sampling volume or duration, alert and action limits and corrective action including investigation should be established in each manufacturing area based on risk assessment. These limits should be routinely reviewed as part of QRM.
1720 - 1722	**Comment:** Changes for clarity in the text. **Proposed change (if any):** Where aseptic operations are performed, microbiological monitoring should be frequent using a combination of methods such as air and surface sampling, (e.g. swabs and contact plates) including glove sampling.
1728 - 1733	**Comment:** The drive for continuous monitoring within a Grade A environment will ultimately require Alternative Microbial Methods and new site defined limits. To expect this in lower risk Grade B areas is currently excessive and impractical. At present, it is felt that the language used allows for airborne samples to be taken continuously throughout the process duration although immediate results would not be required. **Proposed change (if any):** Continuous monitoring in grade A areas should be undertaken for the full duration of critical processing, including equipment (aseptic set up) assembly and filling operations (i.e., an. understanding of function and interactions of each clean area). The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations is avoided. The frequency and type of monitoring in grade B areas should be based on QRM.
1735 - 1736	**Comment:** Change “Rapid” to “Alternative”. Rapid infers that the same data will be available in a shorter period of time, Alternative implies that the data may be different to traditional and therefore require QRM to determine alert and action levels. **Proposed change (if any):** Alternative microbial monitoring methods may be adopted after validation as long as they are demonstrated to be at least equivalent to the established methodology
1744 - 1748	**Comment:** The levels are established through site observations and not regulatory data; therefore, level is suitable.

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): Recommended action levels for microbial contamination are shown in Table 6
1768 - 1772	**Comment:** Allowed non-critical Grade B environments to be eased, where risk is lowered. Defined by QRM, this also allows for genus level identification for those that are determined to be non-objectionable. **Proposed change (if any):** If microorganisms are detected within a critical process in either a grade A or B zone, they should be identified to species level and the impact of such microorganisms on product quality (for each batch implicated) and state of control should be evaluated. Consideration may also be given to the identification of non-critical Grade B and grade C and D contaminants and the requirements should be defined in the contamination control strategy based on QRM.
1806 - 1811	**Comment:** From an aseptic point of view, the APS cycle duration is not a critical parameter during the lyophilization process. The integrity of the freeze dryer is part of the equipment qualification and is routinely verified by leak testing. Most time of the lyophilization process, the lyophilizer is in vacuum status. After reaching the vacuum set point, a static status inside the lyophilizer is given resulting in negligible air flow inside the lyophilizer chamber. Therefore, an increased contamination risk based on the cycle duration in the closed freeze dryer is not given. The potential higher air flow during partial vacuum conditions compared to vacuum conditions inside the lyophilizer, can be considered as worst case for APS. Generally, the filled units should be incubated as soon as possible after filling to assure growth of potentially stressed germs. The possibility to detect growth in the media is contradictive to the time length the units are exposed to the conditions in the lyophilizer. **Proposed change (if any):** The process simulation test for lyophilized products should include the entire aseptic processing chain, including filling, transport, loading, chamber dwell, unloading and sealing. The process simulation should duplicate the lyophilization process, with the exception of freezing, and sublimation, including partial vacuum ~~and cycle duration~~ and parameters as appropriate for the media. Boiling over or actual freezing of the solution should be avoided
1813-1820	**Comment:** Section 9.36 (a) and (b) is unclear as to frequency and number of interventions, and may lead to misinterpretation. Modify to clarify intent and allow for risk based approach. **Proposed change (if any):**

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')*
	The process simulation testing should ~~take into account various aseptic manipulations and interventions known to occur during normal production as well as worst-case situations including~~: include inherent and corrective interventions determined based on a risk assessment and where appropriate, proportional to how often they occur during routine production.
1834 - 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):** b) Determining the representative sizes of container/closure combinations to be used for validation. 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 configuration.
1845	**Comment:** Focus on microbiological contamination in the APS. From a microbiological perspective “any” cannot be scientifically justified. **Proposed change (if any):** e) Ensuring that ~~any~~ microbial contamination is detectable
1882 - 1889	**Comment:** The three per shift requires 9 passing results, where 3 should be sufficient. For a multi-product facility, what is the definition of an “aseptic process”? Provide clarification or allowances for a bracketing approach to bracket worst-case conditions such as container-closure size, etc., as it is impossible to perform media fills every six months for all configurations. **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 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.
1911 - 1918	**Comment:**

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')*
	3 consecutive pass results repeat the above section. In the current Annex 1, revalidation required in case of 2 contaminated units for filling of >10.000 units. **Proposed change (if any): No change** The target should be zero growth and any contaminated unit should result in an investigation (refer to clause 9.47) to determine the root cause (if possible) and to identify appropriate CAPA. Following implementation of CAPA, a repeat APS will be required to validate the effectiveness of the CAPA. The number of APS to be repeated should be determined using QRM principles taking into consideration the number and type of CAPA and the level of contamination found in the failed APS. Typically, 3 successful consecutive repeat APS would be expected; any differences to this expectation should be clearly justified prior to repeat performance.
1925 - 1930	**Comment:** Changes for clarity in application. Discharging into clear containers is risky due to potential contamination issues. **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. 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
1932 - 1933	**Comment:** *"All products that have been manufactured on a line subsequent to the process simulation should be quarantined until a successful resolution of the process simulation has occurred."* The filling line would not be used for commercial applications until fully validated. The statement is redundant. **Proposed change (if any):** ~~*"All products that have been manufactured on a line subsequent to the process simulation should be quarantined until a successful resolution of the process simulation has occurred."*~~ Remove

QC control

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')*
1975	**Comment/rationale:** Is this a requirement for at least grade D as a background for sterility test isolators? If yes, it would be better to state explicitly. Proposed change If not, we propose the rewording as follows: *"The sterility test should be performed under aseptic conditions, which are at least consistent with the standard of ~~clean room~~ environment cleanliness class required for the aseptic manufacture of pharmaceutical products".*
1996 - 1997	**Proposed change:** *"Validation data should demonstrate that ~~A~~any process (e.g. VHP) used to decontaminate sterility samples prior to testing should not negatively impact the sensitivity of the test method".*

Glossary

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')***
2011-2251	**Comment:** Include a definition of "control strategy" in the Glossary which is aligned to ICH Q10 **Proposed change (if any):** Control Strategy - 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.
2011-2251	**Comment:** Include a definition of 'contamination' in the Glossary which is aligned to ICH Q7A **Proposed change (if any):** Contamination - The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens), or of foreign particle matter, into or onto a raw material, intermediate, drug substance or drug product during production, sampling, packaging or repackaging, storage or transport' with the potential to directly adversely impact product quality
2013	**Comment:** There is no need for mentioning the size of the airlock **Proposed change (if any):** Air lock - A ~~small~~ room with interlocked doors,
2018	alert level: defined value lower than action level, resulting from a monitoring which gives, early enough, the signals of a deviation from specified conditions
(ligne 2023)	action level: defined value resulting from a monitoring that should requires appropriate investigation and corrective action.
2030 - 2032	**Proposed change:** *"Aseptic Processing Facility - A building, or segregated segment of it, containing cleanrooms in which air supply, materials, personnel and equipment are regulated to control microbial and particle contamination".*

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')*
2048-2049	There are also barriers in conventional clean rooms. RABS and isolator differentiate by **restricted access**! but not by barrier **Proposed change:** Barrier - A physical partition that affords aseptic processing area (grade A) protection by fully or partially separating it from the surrounding area such as curtains, RABS or isolators.
2076-2087	**Comment:** 2076 Clean Non Classified (CNC) area - An area that does not meet any of the formal pre 2077 determined grades of cleanliness included in the Annex, i.e. grades A to D, but where a 2078 manufacturer defined level of microbial control is still required. The area should be subject to 2079 a formal cleaning/disinfection regime and formal environmental monitoring program to 2080 achieve the defined level of control. The level, type and frequency of both the cleaning 2081 program and the environmental monitoring program (including contamination limits) should 2082 be based on a formal risk assessment (captured within the wider contamination control 2083 strategy) and should be commensurate with the specific risks to the processes and product 2084 performed manufactured within each CNC area. 2085 2086 It is possible that different CNC areas within the same facility may have different approaches 2087 to control and monitoring, based on differing risks to processes and products. New requirement to set up a monitoring program in CNC areas as well implementing also to establish limits for viables and non viables. It will impact the flexibility of the facility and what are then the differences between Class D and CNC? **Proposed change (if any):** Remove the requirement for a monitoring program for CNC
2076-2084	**Comment:** As the definition for Clean Non Classified (CNC) area are not aligned with the ISPE definition which is widely used in the pharma industry it is recommended to clarify the definition and in relation to the material airlock only talk about not classified areas. The term is only mentioned on line 390, and we propose that it is changed there as well (see separate comment) **Proposed change (if any):** (omit CNC definition from document) ~~Clean Non Classified (CNC) area - An area that does not meet any of the formal predetermined grades of cleanliness included in the Annex, i.e. grades A to D, but where a manufacturer defined level of microbial control is still required. The area should be subject to a formal cleaning/disinfection regime and formal environmental monitoring program to achieve the defined level of control. The level, type and frequency of both the cleaning program and the environmental monitoring program (including contamination limits) should be based on a formal risk assessment (captured within the wider contamination control strategy) and should be commensurate with the specific risks to the processes and product performed manufactured within each CNC area.~~ Clarify the CNC definition with the understanding of EM or as in the EMA definition propose different grades of CNC. 1/2/3

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')***
2120	Next to chemical decontamination there also physical decontamination exists such as E-Beam **Proposed change:** Decontamination - A process that eliminates viable bioburden via ~~use of~~ chemical ~~agents~~ or other techniques Consider use of Disinfection wording instead of decontamination
2145	**Comment:** Annex makes use of both the terms "grade A supply" and "grade A air". To avoid misinterpretation we propose to pick one consistent term. **Proposed change (if any):** Change all references to "~~*grade A air*~~" to "***grade A supply***" throughout document.
2146-2147	✓ 11 Glossary: "HEPA filter - High efficiency particulate air filter with minimum 0.3 µm particle retaining 2150 efficiency of 99.97 percent." **Comment:** In ISO 14644, the filtering efficiency is based on MPPS. The definition of HEPA in "11. Glossary" is different from one in ISO 14644 & 29463. **Proposed change (if any):** "and clean air devices" should be deleted.
2177-2178	**Comment/rationale:** Is keeping the "Laminar flow" definition in the glossary still needed? According to us, it is misleading and create confusion as well as "individual" interpretation of the text. It is better to define a physical concept in a single definition. Therefore, our proposal is for keeping only "Unidirectional flow", also used throughout the Annex.
2177	Comment: "Laminar (air) flow" is not a representative scientific term for air flow patterns in clean room conditions. The term "unidirectional" is more appropriative, as well as aligned with FDA. **Proposed change (if any):** Change all references to "~~*Laminar (air) flow*~~" to "***Unidirectional (air) flow***" throughout document.
2177-2178 And 2240-2242	✓ Normally, such conditions are provided by a localised air flow protection, such as laminar air flow work stations or isolators. Unidirectional air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value), the point at which the air speed measurement is taken should be clearly justified in the protocol. ✓ Laminar flow - An airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight line vector. ✓ Unidirectional flow - An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particles away from the critical processing or testing area. **Comment:** The definition of" Laminar Air Flow" and" Unidirectional Air Flow" are confused. Laminar flow. Those terms should be unified to be "Unidirectional air flow". **Proposed change (if any):**

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')*
	Normally, such conditions are provided by a localised air flow protection, such as unidirectional air flow in work stations or isolators.
2184-2185	Scientifically wrong, lyophilization and freeze drying are not the same thing. Proposed change Lyophilization, **in the context of this document, is used synonymously to the term freeze-drying**, A physical-chemical drying process designed to remove solvents from both aqueous and non-aqueous systems, primarily to achieve product or material stability. Lyophilization is synonymous to the term freeze-drying
2205-2215	**Comment:** Opportunity to align Annex 1 definition of RABS to the ISPE definition of RABS. Specifically, with respect to operating as 'doors closed' and 'door opened'. Annex 1 definition of RABS: Restricted Access Barrier System (RABS) - A restricted access barrier system (RABS) provides an enclosed, but not closed, environment meeting defined cleanroom conditions using a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment. Active RABS: integral HEPA-filtered air supply Passive RABS: air supply by ceiling mounted HEPA-filters. Open RABS. Where there are vents in the barrier that allow air to move from the grade A to the grade B area. ISPE Definitions of RABS: (1) An advanced aseptic processing system that can be utilized in many applications in a fill-finish area. RABS provides an enclosed environment to reduce the risk of contamination to product, containers, closures, and product contact surfaces compared to the risks associated with conventional cleanroom operations. RABS can operate as "doors closed" for processing with very low risk of contamination similar to isolators, or permit rare "open door interventions" provided appropriate measures are taken. (2) An aseptic processing system that provides an enclosed, but not closed, environment meeting Grade 5 conditions utilizing a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment. • RABS, Active RABS using an integral HEPA-filtered air supply to the critical area and manual high-level disinfection, usually with Sporicidal agents. Gloves and transfer ports are used for manipulation and commodity addition. • RABS, Passive RABS wherein the airflow to the critical area is provided by ceiling-mounted HEPA filters extending laterally outside the enclosure, and the bottom of the enclosure is open to provide for air flow through the system. Gloves and transfer ports are used for manipulation and commodity addition. Consider using this table to clarify RABS definition

Term	Design Terminology	Operation Terminology
Passive	Unidirectional Airflow Supplied by Cleanroom Ceiling	n/a
Active	Unidirectional Airflow Supplied by RABS Unit	n/a
Open	Air from Inside RABS Exhausts to Surrounding Cleanroom	Open Door Interventions Permitted
Closed	Air from Inside RABS Recirculates in RABS Unit	No Open Door Interventions are Permitted (After Initial Set-up)

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')*
	<table><tr><td>Locked</td><td>n/a</td><td>Doors Unlocked via HMI's; All Interventions Are Recorded</td></tr></table>
2217	**Comment:** In the scope section, it is described that the document is valid for both sterile products and sterile API's. Through the document the individual requirements are described as though the requirement is for sterile products. However, in the glossary section only sterile products are mentioned, and the definition does not include sterile API. In order to improve the reading of the document and avoid misinterpretations, we suggest that sterile API are defined, and the requirements reflects if an individual requirement are valid for sterile product or sterile API or both. **Proposed change (if any):** Add definition of "Sterile API"
2240	**Comment/rationale:** Why not using for unidirectional flow the ISO 14644-3 definition, i.e. "Controlled airflow through the entire cross-section of a clean zone with a steady velocity and approximately parallel streamlines"?
No lines	Definitions requested throughout the document
	alert limit: specified value lower than action limit defining the maximum acceptance threshold of a process variable which gives, early enough, the signals of a deviation from specified conditions
	action limit: specified value defining the maximum acceptance threshold of a process variable beyond which no process action could be performed and formal curative action is required
	Disinfection: reduction of the number of viable microorganisms on a surface product to a level previously specified as appropriate for its intended further handling or use
	(Bio-)decontamination: Operation, delivering momentary result to eliminate, kill or inhibit undesirable microorganisms, limited to those present at the time of the operation, according to the objectives set
	Water for injection definition can be fined in pharmacopoeia
	Purified water: Purified water is obtained by distillation, ion exchange, reverse osmosis or other appropriate processes from drinking water"
	Pure steam: Steam used for sterilization processes should be compliant with Pharmacopoeia such that its condensate meets the specifications of WFI
	Quality Risk Management: Application of data, SME knowledge, and output of quality risk assessment to make risk-based decisions or use a risk-based approach
	Risk:
	Risk Assessment A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
	Sanitization
	Sterilization
	Competent person
	Contamination:The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogens), or of foreign particle matter, into or onto a raw material, intermediate, drug substance or drug product during production, sampling, packaging or repackaging, storage or transport' with the potential to directly adversely impact 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')*
	Contamination Recovery Rate: Time required for an installation to have airborne coming back to at rest situation. Consider guide value as 10 20 min.
	Control strategy: 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.
	Grade A
	Grade B
	Grade C
	Grade D
	In operation:
	At rest:
	Inherent intervention
	Intrinsic sterility