SECOND TARGETED STAKEHOLDER CONSULTATION

GMP
Revision on Annex 1
Manufacture of Sterile Products

1. Introduction

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of the Annex 1, it was found necessary to engage with stakeholders in a second targeted consultation on the updated draft guidance, version 12.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

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

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

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

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

3. Name and contact details of the reviewing organisation

International Society for Pharmaceutical Engineering (ISPE)
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4. Comments

Please write your comments using the spreadsheet below

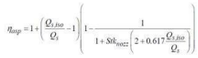
Line number (s)	Comments	Suggested text	Justification
2.1. Feedback on the concerns raised by stakeholders			
Chapter 4	**Qualification & requalification of Clean Rooms**		
392-394	Deletion of reference to Annex 15 and additional text are recommended for clarity and flexibility	4.26 Cleanrooms and clean air equipment should be qualified using methodology in accordance with current GMP requirements. ~~of Annex 15~~ **Initial** cleanroom qualification (including classification) should be clearly differentiated from routine operational environmental monitoring**For limits, refer to Tables 1 and 2 for qualification and Tables 6 and 7 for routine operational monitoring.**	We suggest avoiding use of references linked to Europe only or Regional Regulatory requirements as this document is intended to be used by many regulatory authorities and industry stakeholders around the world. Clarification is recommended that initial cleanroom qualification is clearly differentiated from routine monitoring. However, it should be expected that requalification could include routine monitoring data generated during the prior time interval as this is directly applicable dat The use of a risk based approach / risk assessment tools should be used in the contamination control strategy (CCS) and requalification of the clean room.
396-417	Deletion of reference to Annex 15 and changes to text are recommended for clarity and flexibility	4.27 Cleanroom Qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. As part of the qualification requirements of current GMP ~~Annex 15~~, the qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation): i. Installed filter leakage and integrity testing. ii. Airflow measurement ~~Volume and velocity~~ V**olume for all classifications and velocity for unidirectional airflow areas**. iii. Air pressure ~~difference~~ **differential** measurement. iv. Airflow direction and visualisation**for unidirectional airflow areas**. v. Microbial airborne and surface contamination. vi. Temperature measurement. vii. Relative humidity measurement. viii. Recovery testing. ix. Containment leak testing**for isolators and closed restricted access barrier systems (RABS) (if applicable).**	We suggest removing reference to Annex 15. This paragraph requires clarification linked to ISO 14644. ii. velocity should only be necessary where unidirectional airflow is required. This is consistent with Table 3. iii. Common terminology. iv. these should only be necessary where unidirectional airflow is required. This is consistent with velocity requirement that is aligned with airflow in 4.32, lines 469-470 (airflow velocity and visualization are necessarily linked for the same purpose - unidirectional airflow). ix. Clarification. Standard cleanroms and open RABS are not applicable.
424-437	Major changes of text and table are proposed to align better with ISO 14644.	4.29 For cleanroom classification, the airborne particulates equal to or greater than 0.5 and 5 µm should b measured. For Grade A zone and Grade B at rest, classification should include measurement of particles equal to or greater than 0.5 µm; however, measurement using a second,larger particle size, e.g. ~~,~~ ~~or~~ 5 µm in accordance with ISO 14644 may be considered. This measurement should be performed both at rest and in operation for initial classification or after renovation. The maximum permitted airborne particulate concentration for each grade is given in Table 1. (a) For Grade D, in operation limits are not ~~defined~~ **stipulated** here. The company should establish in operation limits based on a risk assessment, and historical data where applicable. (b)In alignment with ISO 14644-1, 5 µ particles may not be used for classification at ISO 5; however, a company may measure them for reference, the reading may be identified with the macro particle descriptor "M".	**Justification in the cell** 1 micron particle counting We agree that it would be good to have two channels observed with different physical behavior of the particles. Per ISO 14644-1, no class limit is scientifically supportable for 5 micron particles in ISO 5 environments; however, the standard does allow for 5 micron particles to counted for information and the count observed can be documented, so long as it is annotated with the Macro Particle descriptor "M". This indicates that the count is informational only for the reasons outlined in footnotes d and ~~f~~ ISO 14644-1. There is no body of knowledge or justification found in literature which suggests that 1.0 micron particle counting would provide any insight into the performance of an aseptic cleanroom which is not provided by 0.5 micron particles. In support of the preceding, note that the difference in mass between 0.5 and 1 micron particles is only 8x versus the 1000x of a 5.0 micron particle. Similarly, the difference in aerodynamic drag for these particles is only 4x versus 100x for 5.0 micron particles. Additionally, due the close similarity of 0.5 and 1.0 micron particles, white light discrete particles counters cannot reliably discriminate between these channels. Although measuring a particle size ≥ 1.0 micron would include the 5 micron particle size measuring, a true differentiation and interpretation is not possible. The variability in readings due to the lack of discrimination would make any data suspect and would not meet expected limits for repeatability of testing. In summary, a **1 micron particle is simply not sufficiently different f**rom a 0.5 micron particle to allow reading both simultaneously, nor can adding this test, with its associated effort and cost, be justified based on data. ISO 8 Operational Requirements Use of the term "Not Defined" has led many to understand that there is no particulate limit for Grade D, in operation. We have observed this misconception on numerous industry on-line forums. We understand the intent, as outlined in Footnote (a), is to assure that operating companies do due diligence and establish appropriate operating limits for Grade D. We suggest that a change of language from "Not Defined" to "To Be Determined" or similar language (e.g. "Not Predetermined", "Not stipulated") would clarify the intent for operating companies to determine the appropriate limits themselves. ISO 5, 5 micron limits Use of the term "Not Applicable" seems to be inconsistent with the previous sentence "For cleanroom classification, the airborne particula equal to or greater than 0.5 and 5 µm should be measured". The intent would appear to be that 5 micron particles are still observed, but sin no class limit is defined in ISO 14644-1, the information is "For Reference" only. We suggest revising this language will make the docum clearer.
439-444	We suggest using this new proposed text for clarification for section 4.30	4.30 For classification of the cleanroom, the minimum number of sampling locations and their positioning can be found in ISO 14644 Part 1. ~~In addition~~ For the aseptic processing room and the background environment (Grade A zone and Grade B area, respectively), **selected** sample locations should also consider ~~all~~ critical processing zones such as the point of fill and stopper bowls. ~~Critical processing~~ **The sample** locations **used for critical processing locations** should **be selected** based on a documented risk assessment ~~and knowledge of the process~~ **considering** the operations to be performed in the area.	This clause is about sampling locations, we suggest the content of this clause should focus on sampling for better clarity.
445-461	We suggest adding this(iv) clause	4.31 iv. **Classification in the "at-rest "state is required at initial construction and after renovation or changes. Additional testing may be carried out if necessary based upon risk assessment**	We have observed confusion in the industry regarding the requirement for, and usefulness of, at-rest testing when facilities are operational.
463-470	Amendment of text is recommended for clarity an	4.32 ~~The speed of~~ The air velocity supplied by unidirectional airflow systems **in grade A** should be clearly justified in the qualification protocol including the location for air speed velocity measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working height (e.g. where high risk operations and product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies executed at rest and in operation should correlate with the air ~~speed~~ **velocity** measurement.	Unidirectional flow may pertain to other than grade A areas, therefore: Please change "unidirectional airflow system" to "unidirectional airflow systems in grade A airflow" to make it clear that these requirements are meant for grade A and not necessarily for any and all unidirectional airflow system. The most suitable velocity range is highly dependent on: •the individual production equipment calling for grade A protection •the individual Unidirectional Air Flow Device, UDAF, supplying air •the geometries of the room in which the equipment and UDAF is situated There is no "one size fits all". Chasing a specific range changes focus from the importance of understanding and evaluating the effectiveness of the flow in terms of protecting the product and critical surfaces. The proof of concept for the velocity is the air flow visualization. The correlation between speed measurements and visualization is key when velocity measurements are used to verify continued compliance with the visualized airflow. The velocity should be measured where measurements are robust and repeatable to be able to make the best possible correlation to the airflow visualization. Please see: https://ispe.org/pharmaceutical-engineering/march-april-2017/why-90-fpm-considered-standard-cleanroom-airflow
493	We suggest adding a note in this paragraph to incorporate gloveless isolator technology.	4.33 **Any automated, gloveless isolators have substantially reduced contamination risks, e.g. by eliminating human interventions via gloves. Therefore, risk based approaches can be applied to demonstrate suitable environmental conditions (Grade A), where traditional monitoring methods could be replaced by alternative active air sampling methods e.g. Rapid Microbio Methods (RMM). The program should be supported by quality risk management and documented in e.g. the CCS, with consideration that sampling should not compromise the critical zone. Limits should be applied using cfu. If new or different technologies are used that present results in a manner different from cfu, the manufacturer should scientifically justify the limits applied and where possible correlate them to cfu**	New section to acknowledge advanced, gloveless isolator systems and to align with Tables 2 and 7.

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	ISO 5	ISO 5	Reference Only	Reference Only
B	ISO 5	ISO 7	Reference Only	ISO 7
C	ISO 7	ISO 8 [3]	ISO 7	ISO 8
D	ISO 8 [3]	To Be Determined [3d]	ISO 8	To Be Determined [3d]

494-513	We suggest amending the text and table for clarification and to allow more flexibility relating to the minimum requirement for requalification.	4.34 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requirement for requalification of cleanroom areas is as follows: Table 3: Minimum test requirements for the requalification of cleanrooms **Grade** / **Determination of the concentration of airborne viable and non-viable particles** / **Integrity Test of Terminal Filters** / **Airflow volume measurement** / **Verification of air pressure difference between rooms** / **Air Velocity test** A / Yes ** / Yes / Yes ** / Yes ** / Yes B / Yes ** / Yes / Yes ** / Yes ** / * C / Yes ** / Yes / Yes ** / Yes ** / * D / Yes ** / Yes / Yes ** / Yes ** / * . (*) For filling zones (e.g. when filling terminally sterilised products) and **unidirectional airflow zones (e.g. surrounding background** to Grade A RABS.) ** The frequency of re-qualification may be reduced to every 3 years, based upon assessment of relevant continuous monitoring (e.g. continuous pressure monitoring as surrogate for pressure verification and continuous airflow monitoring as surrogate for airflow verification) and environmental monitoring data. **For open aseptic processing or RABS, the recommended time interval for requalification is approximately 6 months.** For **other** Grade ~~A & B~~ areas, the ~~maximum~~ **recommended** time interval for requalification is **approximately** 12 months. For Grade C & D areas, the maximum **recommended** time interval for requalification is 12 +/-1 months. **Further extension of this interval may be justified by testing results and risk assessment**. Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify any out-of-compliance equipment or facility condition or after **significant** changes to equipment, facility or processes **which may impact cleanroom or clean zone performance.**	Frequency of Testing and Activity versus Grade We suggest that the frequency of qualification and testing focus on the activity, rather than the grade of a space - hence the use of double asterisk with modificatiions to the text. Focusing qualification activities to every 6 months only in the aseptic processing room differentiates between the critical processing (e.g. filling) Grade A and B background versus other Grade B spaces (e.g. corridors, storage rooms, etc). This would also more closely align with other global regulation (e.g. FDA). The environmental monitoring (EM) program in a turbulent flow cleanroom acts as a control to capture significant failures of any and all filters since the flow is distributed across the room. * The phrase "background to Grade A RABS" may be interpreted as meaning the entire Grade B room surrounding the RABS, rather than just at the downflow area protecting RABS doors or openings. Velocity would not be a useful measurement in the surrounding non-unidirectional flow rooms (Grades B, C, D). Furthermore, velocity is a useful surrogate to confirm airflow visualization testing in any unidirectional airflow is performing as tested. The addition of the word "approximately" to the 6 and 12 month max time better aligns with sections 9.40 and 9.41 of this Annex, for the more critical process simulation. It is also more practical to allow requalification to be scheduled to fit shut-downs, vacation and national holidays so a tight annual/biannual schedule would in effect change the planning from year to year. Six (6) months has always been a target, never a maximum. Unidirectional Flow vs Turbulent (or Mixed flow) Cleanrooms We suggest that both Grade A and Grade A air supply (which includes terminally sterilized product filling) should be tested as outlined for aseptic processing rooms. The requirement for RABS background appears misleading. Where a unidirectional flow (Grade A air supply) zone surrounds a RABS the air velocity is both meaningful and should be verified. The balance of Grade B space surrounding a RABS would not be meaningful. The requirement for requalification does not explicitly tie to changes which impact cleanroom/zone performance. We believe that this should be explicit. We think use of the double asterisk text is helpful. Air Volume Measurement Technical clarification, air volume measurement may be achieved using either a flow measuring station, "flow hood" or face velocity measurement times the face area.
Chapter 6	**Handling of Water Systems**		
633-638	We suggest modifying the text as in the suggested part to align with practicalities. We suggest as well giving a definition of air velocity	6.7 Water treatment plant and distribution systems should be designed, constructed and maintained to minimize the risk of particulates, microbial contamination/proliferation and pyrogens (e.g. sloping of piping to provide complete drainage and **the avoidance minimizing of** dead legs), and **prevent minimizing** the formation of biofilms to ensure a reliable source of water of an appropriate quality. When filters are included in **pretreatment part or purification part of** the system, special attention should be given to the monitoring and maintenance of these filters. Water produced should comply with the current monograph of the relevant Pharmacopeia.	Following the glossary definition for dead legs it can be difficult to avoid such deadlegs. Risk management and procedures will be used accordingly. Filters can be part of the pre-treatment part and this need to be underline. Water treatment plants in general are not able to get drained for all purification steps. Conservation of systems should also be an option (e.g., for RO). For biofilm we suggest using the term "minimizing" as it is impossible to avoid biofilm in some parts of the systems (before RO or Pretreatment).
640-641	Water generation, distribution and storage are processes which should be validated; qualification (as understood in Annex 15) is not sufficient.	6.8 Water systems should be qualified and the **generation, distribution and storage of water should be validated** to maintain the appropriate levels of physical, chemical and microbial control **taking** Seasonal variation **should be taken** into account **for pre treament systems**. **Ongoing / continued process verification should ensure that the validated state of the water system is maintained throughout its lifecycle**.	Seasonal variations do not impact purified or WFI system but does impact pretreatment.
643-644	We suggest considering editing the turbulent regime modification	6.9 Water flow should ~~remain~~ **be primarily** turbulent through the pipes to minimize the risk of microbial adhesion, and subsequent biofilm formation.	Some operations may result in non-turbulant water flow for very short periods of time.
646-651	We suggest considering the following additions to the text for clarification	6.10 Water for injections (WFI) should be produced from water meeting specifications that have been defined during the qualification process. WFI should be stored and distributed in a manner which minimizes the risk of microbial growth ~~(for example by constant circulation at T° above 70°C)~~ ~~WFI is produced by methods other than distillation, further techniques such as nanofiltration and ultra-filtration as well as electrodeionization (EDI) should be considered in conjunction with reverse osmosis (RO) membranes.~~ **WFI is produced by distillation or by a purification process that is equivalent to distillation, Reverse Osmosis, which may be single-pass or double-pass coupled with other appropriate techniques such as electrodeionization (EDI), ultrafiltration or nanofiltration.**	We suggest removing example of water circulating at 70°C, this could be considered in an other clause dedicated to sanitizing methods. To avoid confusion we suggets using the wording used in the Pharmacopoeia could bring more clarity.
653-655	We suggest using the following rewording	6.11 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should be **steril~~ized~~, and saniti~~z~~ed** and the integrity of the filter tested before installation and after removal following use.	We suggest removing the requirement of sterilizing the filters, Fitting of filters is a non-sterile operation and hence sanitization is considered sufficient and appropriate. WFI is not a sterile fluid and is controlled and monitored to give assurance of compliance with the necessary requirements. Testing after removal of the filters should be based on risk assessment
657-661	We suggest using the proposed rewording We suggest if this clause is dedicated to WFI to remove regeneration	6.12 To minimize the risk of biofilm formation ~~sterilization~~ **chemical or thermal disinfection** or regeneration of water systems should be carried out according to a predetermined schedule~~d~~. When microbial counts exceed action limits **the risk of biofilm formation should be assessed and disinfection of the water system should be considered**. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure. Water should be tested after disinfection/regeneration. The **chemical testing** results should be approved before the water system is returned to use.	We suggest removing "sterilisation" for for non WFI water systems, and consider thermal or chemical disinfection or regeneration is appropriate. After disinfection we suggest removing the requirement for having all tests results before returning to use. The processes should be validated. Water systems are highly controlled and monitored. Tests results for approval of water system returning to use could be required on risk based assessment, as some system have thermal disinfection on a reular basis every day. **If this clause relates only to WFI consider removing "or regeneration;"**
663-673	We suggest enhancing CCS in the scope or principle of the document.	6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed. Alert levels should be based on the qualification or a review of ongoing monitoring data that will identify an adverse trend in system performance. Sampling programs should reflect ~~the requirements of the CCS and include:~~ i. All points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis. ii. Potential worst case sampling locations . ~~iii. A sample from the point at the end of the distribution loop each day that the water is used~~.	We suggest removing iii. Microbial samples from this location do not represent the points where the water is actually used in production. Chemistry of water systems is considered to be evenly mixed, so a sample that represents the distribution loop can be collected anywhere in the distribution loop or measured with online instrumentation installed anywhere in the distribution loop. The full system will be assessed . the sampling will cover the worst case . We suggest enhancing CCS discussion in the scope and principle of the document to cover the whole document. This will avoid references to CCS requirements in some part of the document.
675-679	We suggest using the following proposal	6.14 ~~Breaches of~~ Alert level **excursions** should be documented and reviewed, and include investigation ~~of system trends~~ to determine whether the ~~breach~~ excursion is a single (isolated) event or if results are indicative **of an adverse trend,** ~~of~~ loss of control or system deterioration. Each ~~breach of~~ action ~~limits~~ **level excursion** should be investigated to determine the root cause of the issue and any impact on the quality of products and manufacturing processes as a result of the potential use of the water.	We suggest replacing "Alert level excursions" instead of "Breaches of alert levels". Investigation should not only be limited to system trends. "Action level excursion" instead of "Breach of action limit".
683-684	We suggest removing 'sterilisation' for water systems, and consider thermal or chemical disinfection	6.15 WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity, (unless justified otherwise) as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk ~~and the outcome of qualification.~~	We suggest deleting the statement "and the outcome of qualification." as the location of sensor is defined at the design phase of the system based on risk assessment.
Chapter 8	**Handling of sterilizing filter including pre-use post sterilization integrity testing (Pupsit)**		
1492-1494	We suggest remove the example of very small volumes.	8.88 …..sterilization integrity testing (PUPSIT) may not always be possible after sterilization due to process constraints ~~(e.g. the filtration of very small volumes of solutions~~ e.g **unacceptable risk to the sterile boundary**)	We suggest widening the example to 'unacceptable risk to the sterile boundary' rather than limiting it to very small volume solution.
1540-1541	We suggest replacing "lot" by "batch".	8.95 Liquid sterilizing filters should be discarded after the processing of a single ~~lot~~ **batch** and the same filter should not be used for more than one working day unless such use has been validated.	We suggest replacing "lot" by "batch" since the Annex uses "batch" or "batch/lot"
1542 - 1543	We suggest clarifying the content of this clause that "campaign" refers to multiple batches of the same product with one filter	8.96 Where campaign **(multiple batches)** manufacture of a product has been appropriately justified ~~in the CCS~~ and validated, the user of the **sterilizing** filter should:	We suggest defining in the glossary the term of Campaign (multiple batches) for aseptic processes and removing the reference to CCS which should be covered throughout the document.
Chapter 8	**Handling of Lyophilizers**		
1654-1658	We suggest considering that holding time should consider time between sterilzation cycle and use rather than between sterilization cycle	8.111 The sterilization of lyophilizers and associated equipment, (e.g. trays, vial support rings) should be validated and holding times between sterilization cycles **and use** appropriately challenged during aseptic process simulations. The lyophilizer should be sterilized regularly, based on system design. Re-sterilization should be performed following maintenance or cleaning. Sterilized lyophilizers and associated equipment should be protected from contamination after sterilization.	We suggest that "holding time" be regarded as time between sterilization and use of the equipment rather than between two sterilisation cycles.
1665-1669	Batch certification is considered an European concept.	8.113 The integrity of the lyophilizer system should be maintained following sterilization and during use. The filter used to maintain lyophilizer integrity should be sterilized before each use of the system and its integrity testing results should be part of the batch ~~sterilization~~ **record and checked for compliance**. The frequency of vacuum/leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.	We suggest removing batch certification. Certification seems a European concept.
Chapter 10	**Sterility testing**		
2294-2297	Modification of text recommended for clarity and flexibility.	10.6 i. For products which have been filled aseptically, samples should include containers filled at the beginning, middle and end of the batch ~~and after any significant intervention (e.g. interventions where the integrity of a barrier is breached (open door)) or an operator intervention into critical zones~~. **Additional samples should be considered for significant unplanned interventions where there has been potential to breach sterility assurance.** (e.g. discard strategy, APS)	We suggest not requiring additional sampling where intervention are covered by successfull APS. In the glossary "Critical intervention" could be corrective or inherent we suggest that inherent interventions do not require additional sampling.
2.2. Sections and /or paragraphs which were substantively modified			
Chapter 4	**Definition and Handling of barriers systems**		
322-325	We suggest incorporating requirements for RABS based on CCS	4.18 Isolator or RABS ~~-~~technologies, and the associated processes, should be designed to provide protection of the Grade A environment. **For Isolators** the entry of materials during processing (and after ~~decontamination~~ disinfection) should be minimized ~~supported by~~ **and preferably supported by rapid transfer technologies or transfer isolators.** **For RABS introduction of materials requiring disinfection should be avoided.**	This clause addresses only isolators, it cannot be used for RABS. This clause needs some additional clarification for RABS. We suggest this clause could be divided in two parts one for isolators, the second for RABS. A risk based approach would be helpful to cover RABS technology.
332-340	We suggest that "unidirectional airflow" is replaced by "first air protection".	~~4.20 The critical zone of the RABS or open isolator used for aseptic processes should meet Grade A requirements with unidirectional airflow.~~ In closed isolator systems where airflow may not be unidirectional, it should provide Grade A conditions and be demonstrated to provide adequate protection for exposed products during processing. The design of the RABS and open isolators should ensure **Grade A requirements with first air protection and** a positive airflow from the critical zones to the surrounding background environment; (unless containment is required in which case localized air extraction is required to prevent contamination transfer to the surrounding room). Negative pressure isolators should only be used when containment of the product is considered essential and risk control measures are applied to ensure the critical zone is not compromised	Unidirectionality vs First Air Unidirectional flow is only one way of achieving environmental control. The term "first air" may address the potential conflict in this section. Additionally, "unidirectionality" cannot be proved close to an obstruction (e.g. a conveyor) due to the formation of a boundary layer and turbulent zone directly above the boundary layer. We understand the intent to be to prove protection from end-to-end and side-to-side of the Grade A zone, but the ability to prove unidirectionality at all heights is neither possible, nor necessary. We suggest that proving "first air" is more meaningful as it shows protection of the zone by filtered air
344-345	We suggest adding in line 344: airflow studies may be one way of documenting this point, other methods may apply.	4.21…. **Qualification studies** (e.g.Airflow studies) should be performed to demonstrate the absence of air ingress during interventions ~~such as door opening~~	We suggest not limiting the studies to air flow (e.g.smoke tests) as other techniques may be used. We suggest removing or make a clarification "such as door openings"… This is misleading and suggest that opening a door in a RABS is accepted.
353-362	We suggest switching 4.23 and 4.24 as decontamination and disinfection are clarified in 4.24 and used in 4.23. We suggest some changes as integrity testing for RABS is not feasible.	4.23 The materials used for glove systems (for both RABS and isolators), as well as other parts of an isolator, should be demonstrated to have good mechanical and chemical resistance. i Integrity testing of the ~~barrier systems~~ **isolator**, and leak testing of the glove system ~~and the isolator~~ should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined periods ~~at a minimum~~ at the beginning and end of each batch, and should include a visual inspection following any intervention that may affect the integrity of the system. For single ~~unit~~ batch sizes, integrity may be verified based on other criteria, such as the beginning and end of each manufacturing ~~session~~ **period** . ii RABS gloves used in Grade A zone should be sterilized before installation. RABS gloves used in Grade A zone ~~and sterilized (or effectively decontaminated~~ **should be sanitized** by a validated method ~~which achieves the same objective~~) prior to each **subsequent** manufacturing campaign. iii For **barrier systems** The frequency of glove replacement should be defined within the CCS.	We suggest for clariying of the document to separate this clause into two parts with one part addressing isolators and the other adressing RABS. All requirements cannot be applied to both systems.

365-381	We suggest as previous paragraph to switch 4.23 and 4.24 for a better understanding as decontamination and disinfection are described in 4.24.	4.24 For RABS and isolator systems, decontamination methods should be validated and controlled within defined cycle parameters. The cleaning process prior to the disinfection step is essential; any residues that remain may inhibit the effectiveness of the decontamination process: i. For isolators, the decontamination process should be automated~~and~~ **The sanitizing st**ep should include a sporicidal agent in a suitable form (e.g. gaseous, aerosolized or vaporized form) to ensure thorough microbial decontamination of its interior. Decontamination methods (cleaning and sporicidal disinfection) should render the interior surfaces and critical zone of the isolator free of viable microorganisms. ii. For RABS systems, the disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly disinfect the interior and ensure a suitable environment for aseptic processing. Evidence should also be available to demonstrate that the agent used does not have adverse impact on the product produced within the RABS or isolator. The holding time before use of these systems should be validated.	As decontamination process is the combination of cleaning plus disinfection it is sugggested these 2 steps be identified for isolators.
Chapter 6-8	**Gas Filters**		
710-713	We suggest incoporating as well the possibility of campaign production	6.19 Where the filter is used on a batch**or campaign** basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results included as part of the~~batch certification process~~. **record and checked for compliance**	Batch certification is defined in Annex 16 Eudralex vol 4. We suggest using "checked for compliance" as beng more appropriate in this case.
1517-1521	We suggest some changes of text for flexibiity	8.90 The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals. Where gas filters are in place for extended periods such as vent filters, integrity testing should be carried out ~~pre and~~ **at least** post-use. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses an~~sterilization~~ **disinfection** cycles permitted).	For non critical air or gas filters, pre and post use integrity should remain under the company CCS and should be at least post use. For non critical air/gas sterilisation is not required and we recommend considering disinfection. Many filters used in compressed air systems are not capable of being integrity tested – eg compressor air inlet filters, coalescing filters, commercial grade particulate filters.
Chapter 7	**Personnel qualification**		
762-765	We suggest clarifying the role of staff doing an APS to be qulified to enter a Grade A/B area.	7.5 The unsupervised access to Grade A zone and Grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful aseptic process simulation (APS)**during which they perform their assigned duties**.	We suggest clarifying this clause for unsupervised access in Grade A and B to staff having made an APS performing their normal duties. Not all staff are doing activities at the most critical part of the process.
823-843	We suggest some wording\clarification for this clause.	7.14 i. Grade A / B: Dedicated garments to be worn under a sterilized suit~~Sterile~~ **Sterilized** headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit. A~~sterile~~ **Sterilized** face mask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particulates. Appropriate sterilized, non-powdered, rubber or ii. 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~~ **clean** shoes or overshoes iii Grade D.....appropriately ~~disinfected~~ **clean** shoes or overshoes should be worn. Appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.	We suggest using in this whole clause the term sterilized for clarity and consistency. Line 834 Clarification is required of two pieces trouser suit. Is it a two layers suit or separate pants and shirt? For grade C and D we suggest replacing "disinfected" by "clean". The whole document is based on QRM and CCS principles, if company CCS requires additional constraints they will be incorporated in the company policy.
846-849	Additional text suggested for clarity	7.15 " .... Facility suits, covering the full length of the arms and the leg**sand personal (or facility)** socks covering the feet, should have been worn before entry to change rooms for Grades B and C. Facility suits **and personal (or facility)** socks should not present a risk of contamination to the gowning area or processes."	We suggest leaving the possibility to have facility socks or personal ones in clean aereas.
851-853	We suggest for better clarity deleting this clause and transfering into 2 existing clauses.7.14 and 7.18	~~7.16 Every operator entering Grade B or A areas should gown into clean, sterilized protective garments (including eye coverings and masks) of an appropriate size at each entry. The maximum duration of each garment use should be defined as part of the garment qualification~~.	We suggest transferring the first sentence of this clause about gown design to clause 7.14, and the second sentence about garment qualification to clause 7.18. In that way, the specific requirement to the gown design and garment qualification are relocated to other areas that also cover these specific topics.
Chapter 8	**Aseptic Prodection**		
935-937	We suggest additional clarification in Table 5.	8.11 Table 5, Row "Grade A": 6th bullet to read: 'Staging and conveying of sterile primary packaging component**when not wrapped**'. 8th bullet to read: 'Loading **and unloading** of a lyophilizer'	We suggest that clarifying that staging and replenishement are required under Grade A area when products are not wrapped. We suggest in the table N°5 incorporating a section for Grade A air supply for Lyophilizers unloading.
945-946	Chemical sterilization for bulk solution should be clarified a little bit more.	8.12 iii. Bulk solutions should be sterilized by a validated process, e.g. by heat, chemical sterilization**(for API)** or via sterile filtration.	We suggest incorpoorating a clarification where using chemical sterilization is required.
950-953	We suggest clarifiaction of air standards for filling line set up.	8.13 The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items **with direct or indirect product contact** should be treaded as an aseptic process and performed in a Grade A zone with a Grade B ackground.**The filling line setup and filling of the sterile product should be treated as an aseptic process and performed in a Grade A zone with a Grade B background.** Where an isolator or RABS is used, the background should be in accordance with paragraphs 4.21 & 4.22.	We suggest defining preparation as the filling line set up and these operations should be covered in the CCS .
998	We suggest combining sub sections 8.18 vi, vii, and viii.	8.18 vi. The aseptic processing time (including the filling time. maximum exposure time of sterilized containers and closures in the critical processing zone (including filling) prior to closure.	We suggest clarifying 8.18 requirement where some points are not clear being a mix of process operation time and holding times. We suggest combining information on holding time and operation duration not separating them in the various sub points. We suggest as example to merge the points vi; vii; viii.
1005-1007	We suggest deleting reference to APS as it is superfluous.	8.19 Aseptic operations ~~(including APS)~~ should be observed at a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations and address inappropriate practices if detected.	We suggest removing reference to APS, which is clearly an aseptic process.
Chapter 8	**Moist Heat sterilisation**		
1230-1233	We suggest amendment to clarify absence of residual water.	8.55 For porous cycles (hard goods) time, temperature and pressure should be used to monitor the process. Each item sterilized should be inspected for damage, packaging material integrity and~~moisture~~ **absence of visual water residues** on removal from the autoclave as far as possible. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.	In the EN285 a mass test load increase of 0.2% is mentioned (chapter 8.3). This means that there is a certain amount of moisture expected and tolerated.
1235-1237	We recommended inclusion of "appropriate" for location of sensor for SIP systems.	8.56 For autoclaves fitted with a drain at the bottom of the chamber, the temperature should be recorded at this position throughout the sterilization period. For steam in place systems, the temperature should be recorded at **appropriate** condensate drain locations throughout the sterilization period.	We suggest for SIP to introduce "appropriate" for the temperature probe location based on the worst case location.
1245-1247	We suggest deletion of "normally weekly"	8.58 Leak tests on the sterilizing system should be carried out periodically~~(normally weekly)~~ when a vacuum phase is part of the cycle or the system is returned, post-sterilization, to a pressure lower than the environment surrounding the sterilized system.	We suggest leaving the determination of leak testing frequency to be based on the QRM principles which covers the whole Annex 1 scope
1249-1253	We suggest deletion of "normally performed on a daily basis"	8.59 There should be adequate assurance of air removal prior to and during sterilization when the sterilization process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle~~(normally performed on a daily basis)~~ or an air detector system. Loads to be sterilized should be designed to support effective air removal and be free draining to prevent the build-up of condensat**in locations that could compromise load sterilization**.	We suggest leaving the determination of the air removal test cycle to be based on the QRM principles which covers the whole Annex 1 scope.
1255-1258	We suggest carifiying this clause. We suggest as well moving this clause before the 8.55 clause. These two are very close in expectations.	8.60 The items to be sterilized, other than products in sealed containers, should be dry, wrapped in a material which allows removal of air and penetration of steam and prevents recontamination after sterilization. All loaded items should be dry upon removal from the sterilizer~~Load dryness~~ **Absence of visual water residue** should be confirmed by**process validation and regular** visual inspection as a part of the sterilization process acceptance.	We suggest leaving the load dryness checking under the QRM principles and clarify that dryness is checked by 'visual water residues' as part of process validation and by regular visual inspection.
1266-1269	We suggest change from "optimal" to "adequate" based on QRM principles.	8.62 Distortion and damage of non-rigid containers that are terminally sterilized, such as containers produced by Blow-Fill-Seal or Form-Fill-Seal technologies, should be prevented by appropriate cycle design and control (e.g. setting~~optimal~~ **adequate** pressure, heating and cooling rates and loading patterns).	We suggest using the term "adequate" instead of optimal. This will be covered by QRM.
1273-1278	Minor revised text suggested for clarity and to reflect the practica situation.	8.63 .....system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilized. ~~These~~ Locations should be demonstrated as being representative of, and**or** correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilized by steam in place it should remain integral and held under positive pressure prior to use.	It is agreed that pressure, temperature and time should be monitored during the SIP process. However, pressure on an SIP system is not monitored at all locations. It is typically monitored at the steam inlet. Temperature sensors or RTDs are used at locations deemed to be either representative or in the worst-case location. As the draft Annex v12 currently reads, it implies that pressure must be monitored at all locations respresentative and correlated to the worst-case locations. This is difficult when pressure is only measured at the steam source supplied to the system being SIP'd. Temperature is a more pratical means of correlating slowest to heat locations
1282-1284	Text recommended for simplifying the clause	8.64 .....There should be routine checks for the sterilizer to ensure that wate~~r nozzles~~ **inlets** are not blocked and drains remain free fromdebris.	
Chapter 9	**Personnel Monitoring**		
2021-2024	We suggest requiring sampling on staff gloves at the exit of Grade A/B areas where aspetic activities takes place. We suggest adding at the end of the clause end of shift for clarity.	9.32 Personnel gloves (and any part of the gown that may potentially have direct impact on the product sterility (e.g. the sleeves if these enter a critical zone) should be monitored for viable contamination after critical operations and on exit from the~~cleanroom~~**Grade A/B area**. Other surfaces should be monitored at the end of an operation**or shift**.	We suggest for this clause clarifying exit of A/B area instead of cleanroom which could be misunterpreted and leading to non required sampling. We suggest clarifying the words end of operation as end of operation can be considered as end of a critical operation or end of the day's work i.e. shift. This clause should be aligned with 9.25.
2026-2031	Microbial monitoring is not sufficient to assess aseptic behaviour. This point is covered also by observation. This point should be linked with clause 8.19.	9.33 At the end of clause 9.33 add a note that reads 'refer also to clause 8.19 above'	Monitoring of aspetic behaviour should be a combination of microbial monitoring and observation by experienced personnel.
Chapter 9	**APS**		
2162-2168	We suggest introducing the concept of "bracketing", based on QRM principles	9.40 .....Normally, process simulation tests (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process aseptic filling line, each filling line and representative of each shift. **Bracketing can be considered**	We suggest incorporating: "Bracketing" in Glossary We suggest introducing Bracketing based on QRM to allow APS covering worst cases in the design of these activities and avoiding for one product 3 batch of each strength of what is the same aseptic operation. A suggested definition of "Bracketing"could be extracted from Annex 15 "A science and risk based validation approach such that only batches on the extremes of certain predetermined and justified design factors, e.g. strength, batch size and/or pack size, are tested during processsimulation. The design assumes that simulation of any intermediate levels is represented by simulation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition. Bracketing can be applied to different container sizes or different fills in the same container closure system."
Chapter 10	**Quality Control**		
Other Significant Comments			
83		2.5	

186-207	Revisions to text are suggested for clarity and practicaity	4.4 For the manufacture of sterile products there are four grades of cleanroom. Grade A zone: The critical zone~~for high risk operations or for making aseptic connections~~**as identified by risk assessment**, ~~by ensuring~~**ensures** protection by first air (e.g. aseptic processing line, filling zone, stopper bowl, open ampoules and vials). Normally, such conditions are provided by a localised airflow protection, (such as unidirectional airflow work stations), RABS or isolators**Where unidirectional airflow is used,** the maintenance of~~unidirectional airflow~~ **first air** should be demonstrated and qualified ~~across the whole of the Grade A zone~~**as protecting open product and critical areas**. Direct intervention (e.g. without the protection of barrier and glove port technology) into the Grade A zone by operators should be minimized by premises, equipment, process and procedural design. Grade B area: For aseptic preparation and filling, this is the background cleanroom for the Grade A zone (where it is not an isolator).~~When transfer holes are used to transfer filled, closed products to an adjacent cleanrooms of a lower grade, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the Grade B~~Pressure differentials should be continuously monitored. Cleanrooms of lower grade than Grade B can be considered where isolator technology is used (refer to paragraph 4.22). Grade C and D area: These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products but can be used for the preparation /filling of terminally sterilized products. (See section 8 for the specific details on terminal sterilization activities). **When transfer holes are used to transfer filled, closed products to adjacent cleanrooms of a lower grade, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the higher grade area.**	Grade A Definition The citation of aseptic connections specifically here could be misleading. This does not recognize the difference between engineered aseptic connectors and open connections. We suggest that the first sentence should focus on the risk assessment's identification of critical zones. Suggest that the tense of "ensure" should be revised. Unidirectionality vs First Air The suggestion of proving unidirectionality in this section may be seen as conflicting with 4.20. Additionally, "unidirectionality" cannot be proved close to an obstruction (e.g. a conveyor) due to the formation of a boundary layer and turbulent zone directly above the boundary layer. We understand the intent to be to prove protection from end-to-end and side-to-side of the Grade A zone, but the ability to prove unidirectionality at all heights is neither possible, nor necessary. We suggest that proving "first air" is more meaningful as it shows protection of the zone by filtered air. This is further supported by the acceptance of non-unidirectional flow isolators in this, and prior, versions of the Annex; as proved in industry and validated to provide aseptic conditions. Additionally, we suggest that reinforcement is required on the concept of "first air", that it is only potentially contaminating obstructions that should be considered in the evaluation of first air, since some obstructions in the airstream are unavoidable (e.g. the air which touches a vial must have passed over the filling needles, while being filled.) Focusing proof of "first air" across the critical zones is superior to "across Grade A" since some areas within Grade A may not be critical (e.g. after sterile capping) verification of "first air" in these areas does not contribute to product quality. Transfer Hole The "transfer hole" reference would apply to Grade A, whenever capping is undertaken outside of the aseptic environment. We suggest that this is made a general statement, applying to both Grade A and Grade B areas. The "transfer hole" reference would apply to Grade A, whenever capping is undertaken outside of the aseptic environment. We suggest that this is made a general statement, applying to both Grade A and Grade B areas.
276-280	We suggest removing solutions from this section.	4.13 Both sets of doors for pass-throughs and airlocks (for material and personnel) should not be opened simultaneously.~~For airlocks leading to a Grade A zone and Grade B areas, an interlocking system should be used. For airlocks leading to Grade C and D cleanrooms, a~~Mechanical interlocking, visual and/or audible warning system should be applied.	We consider GMP defines the requirement, and companies implement with the relevant means.
295-302	Revisions to text are suggested for clarity and practicaity	4.15 Airflow patterns within **aseptic processing** cleanrooms and zones, should be visualised**as part of qualification**. **Grade A and Grade A air supply should** ~~to~~ demonstrate **effective flushing with first air and** that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contaminant to the higher grade areas. **The interfaces between aseptic cleanrooms and zones with surrounding lower grade areas should be visualised, or otherwise tested (e.g. via particle counting)**. Where air movement is shown to be a risk to the clean area or critical zone, corrective actions, such as design improvement, should be implemented. Airflow pattern studies should be performed both at rest and in operation (e.g. simulating operator interventions). Video recordings of the airflow patterns should be retained. The outcome of the air visualisation studies should be considered when establishing the facility's environmental monitoring program.	Unidirectional Flow vs. Turbulent (mixed) Flow Cleanrooms Airflow patterns in Unidirectional Grade A zones and within Grade A airflow are critical to maintain desired conditions. Studies can be designed with objective acceptance criteria (e.g. no refluxing, no ingress from lower grade spaces or reservoir of particles). We agree that these studies are useful when performed in both the at-rest state before operation and in-operation state (usually as part of simulation). Studies of other than Grade A and Grade A air supply clean zones are interesting and useful as engineering studies (to compare actual results to design models) and to assist in the composition of Environmental Monitoring programs to identify areas of risk. These studies are not suitable for proof of cleanroom performance as the flow in these areas is not expected to be unidirectional. The limitation of smoke studies in non-unidirectional cleanrooms is that no objective and meaningful acceptance criterion is practical for airflow visualization. Luckily, adequate means of proving cleanroom performance in Grade B and C are already required within the Annex. The use of both total particulate monitoring and recovery testing (cleanup test) per 4.29 and 4.30 are sufficient to prove room performance. Interface Studies Since Grade B, areas are not necessarily unidirectional and there are no practical acceptance criteria for airflow visualisation studies, other tools can be employed to show protection of these spaces, such as studies at the interface with other grades. Studies via visualization or particle counting assist in understanding the impact of interfaces with other areas on a cleanroom or clean zone. The in-operation (simulative) state is of greater interest for ingress airflow studies as the interfaces may need to be operated in order to create a challenge.
304-312	We suggest removing the first sentence of the paragraph.	4.16 ~~Indicators of pressure differences should be fitted between cleanrooms and/or isolator S~~et-points and the criticality of pressure differentials should be documented within the CCS. Pressure differentials identified as critical should be continuously monitored and recorded. A warning system.	The requirements are adequately defined in the remainder of the section
588-592	Particle counters, including sampling tubing, should be qualified. The tubing length should be no greater than 1 meter with a minimum number of bends and bend radius should be greater than 15 cm. Portable particle counters with a short length of sample tubing should be used for classification purpose. Isokinetic sampling heads should be used in unidirectional airflow systems and should be positioned as close as possible to sample air representative of the critical location.	5.9 Particle counters ~~including sampling tubing~~**using a tubing length greater than 1 meter with more than 2 bends should be qualified and a correction factor applied to the readings where necessary**. **Bends used should have a bend radius greater than 15 cm**. Portable particle counters with a sample tubing **less than 1m** should be used for classification purpos**whenever practical**. Isokinetic sampling heads **(i.e. a sampling head designed to disturb the air as little as possible such that the same particulates go into the nozzle as would have passed the area if the nozzle had it not been there)**, should be used in unidirectional airflow systems and should be positioned as close as possible to sample an representative of the critical location.	There should be a length of tubing below which specific qualification is not called for. Particle counters and installation of them are known to industry and up to 1m tube length is generally accepted to have benign impact on the sampling results. We acknowledge that longer sampling tubes could result in 'fall out' but for some machines – not least filling machines in isolators – being limited to 1m tubing length would result in other compromises that could jeopardize aspects of the environmental quality. Furthermore there are appropriate alternative solutions to the short tube length, for example using a correction factor or an installation geometry that does not result in fall out. Therefore longer sampling tubes for monitoring should be allowed but requested validated. For classification short tubing lengths are the right choice in most cases, but blanket requirement for short tubing could lead to not making the best choice of sampling locations
621	Schematic drawings do not incorporate pipe length.	6.5 i. Pipeline flow direction, slopes***(where relevant)*** *and* diameter~~and length~~. iii. Valves, filters, drains***(where relevant)***, sampling and user points.	We suggest removing requirement of length of pipes on schematic diagrams which are not in engineering practice in 2D drawings.
692-700	Suggest adding: "except for microbial growth since microbial testing of pure steam is not required"	6.17 For a pure steam generator supplying pure steam used for the direct sterilization of materials or product-contact surfaces (e.g. porous hard-good autoclave loads), steam condensate should meet the current monograph for WFI of the relevant Pharmacopeia**except for microbial growth since microbial testing of pure steam is not required.** ~~"These parameters should in case of sterilisation for porous loads include the following: non-condensable gases, dryness value (dryness fraction) and superheat."~~ and replace by: **The following parameters should** ~~include~~ **be considered**: non-condensable gases, dryness value (dryness fraction) and superheat."	The steam condensate must comply to monograph for WFI – this should not be applicable for the microbial (CFU) testing since it is not relevant. The steam is used to kill microorganisms and will as having a default not contain living microorganisms. As mentioned in line 690 the steam quality should meet chemical and endotoxin requirements. The steam quality requirements, e.g. non condensable gases, could be interpreted to apply to all steam sterilisation processes, for example tank/pipe SIP. For these type of processes it does not apply because the gravity will ensure that non-condensable gasses are removed. It should be applicable to loaded sterilisation processes only – e.g. where a pre-vacuum is required. • Regular physical-technical and microbial requalification of sterilization processes is the method of choice to get appropriate direct information on the validation status of the autoclave.
732-733	This clause is not clear enough - we suggest rephrasing it	6.23 When located in cleanrooms, vacuum and cooling systems there should be periodic cleaning/disinfection as appropriate~~determined in CCS~~	As CCS is part of the principles of the Annex 1 we suggest removing reference to CCS in the clauses to avoid having some clauses with and others without.
775-777	Additional clarity for practical reasons is recommended concerning disqualigfication of personnel involved in a failed APS.	7.7 There should be systems in place for disqualification of personnel from entry into cleanrooms based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring program and/or after participation in a failed APS**(if investigation results in personnel being identifed as a root cause of the failed APS)**.	We suggest not disqualifying people involved in a failed APS without making a Risk Assesment and identifying the personnel as root cause for the failed APS
861-862	An additional check is recommended	7.18 …… risk of shedding of particles. After washing and before packing, garments should be visually inspected for damage **and visual cleanliness.**	We suggest adding cleanliness visual checking as an inspection.
1073-1076	We suggest deletion of reference to "fatigue" as it is subjective	8.30.... consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or~~fatigue at the~~ end of shift) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, from inspection should be taken.	We suggest deletion of "fatigue at the" since this is subjective. Validation of the inspection is based on QRM and design of the validation process has to take into account worst cases.
1190-1192	We suggest removing an example for flexibility to allow tachnical progress	8.49 Each heat sterilization cycle should be recorded either electronically or by hardcopy, on equipment with suitable accuracy and precision. Monitoring and recording systems should be independent of the controlling system~~(e.g. by the use of duplex/double probes)~~	We suggest removing the example of duplex or double probes as the technologies are in evolution. The system must have safeguards and/or redundancy in its control and monitoring instrumentation to detect a cycle not conforming to the validated cycle parameter requirements and abort or fail this cycle.
1194-1197	We suggest a change of text for clarity	8.50 The position of the temperature probes used for controlling and/or recording should be**identified during design** and ~~determined~~ confirmed as representing the system during the validation which should include heat distribution and penetration study and, where applicable, also checked against a second independent temperature probe located at the same position.	Control and record probe locations are based on QRM, and specified during the design phase of the equipment.
1298-1316	We suggest changes in text to reflect more accurately the practical situation	8.67 Dry heat sterilization/depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the Grade A sterilizing zone by maintaining pressure differentials and airflow through the tunnel from the higher grade area to the lower grade area~~Airflow patterns should be visualised and correlated with temperature studies. The impact of any airflow change should be assessed to ensure the heating profile is maintained~~. **The pressure cascade in the tunnel should be monitored and correlated with the temperature studies. The impact of any pressure cascade change should be assessed to ensure the heating profile is maintained. For older tunnels without continuous pressure monitoring other measures should be used to confirm the airflow through the tunnel.** All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests should be performed to demonstrate air filter integrity**air quality at 0.5µ** (at least **approximately** biannually).	The flow through the tunnel is ensured by the pressure cascade which is correlated to the temperature studies. The pressure cascade is upheld also at temperature and therefore it is a superior indicator for the validity of the temperature studies, - better than the airflow visualization which can only take place in the cold state. The geometry of the tunnel renders the visualization of the shutter into and out of the heating zone virtually impossible – smoke stick and a mirror on a stick can provide some info, but it is incredibly difficult to produce a film that clearly shows the flow around the shutters for the heating zone. USP 1228.1 has no mention of airflow for validation of sterilizing / depyrogenation tunnels ********** Airflow direction can be verified either with smoke study or continuous monitoring. Integrity testing as outlined in ISO 14644-3 cannot be performed in most tunnels. This is due to inaccessibility of filter media during testing, Air quality can be tested and is more informative. The frequency of testing is not aligned with other sections, "approximately" added to align with 9.20 frequency for APS.
1403-1408	We suggest removing text which should be in a marketing authorisation	8.81 If the product cannot be sterilized in the final container, solutions or liquids should be sterilized by filtration through a sterile sterilizing grade filter~~(with a nominal pore size of 0.22 µm (or less) that has been appropriately validated to obtain a sterile filtrate)~~ and subsequently aseptically filled into a previously sterilized container. The selection of the filter used should ensure that it is compatible with the product and as described in the marketing authorization (refer to paragraph 8.125).	We suggest removing the filter reference example which should be described in the marketing authorisation.
1410-1414	We suggest for clarity removing the reference to a second sterile filtration.	8.82 Suitable bioburden reduction prefilters and/or sterilizing grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the ~~primary~~ sterilizing grade filter. ~~Due to the potential additional risks of a sterile filtration process, as~~ compared with other sterilization processes, a second filtration through a sterile sterilizing grade filter, immediately prior to filling, should be considered as part of an overall CCS.	Sterile filtration design as per scope of the document is based on QRM and CCS will define requirement for 2 sterile filtrations. We suggest not mentioning CCS in the clause to reinforce the statement in the chapter 2 "Principles"
1482-1484	We suggest removing the note.	~~8.83 Note: Results of these checks should be included in the batch record. Any significant difference in parameters from those validated to those observed during routine manufacturing should be noted and investigated.~~	We suggest removing the note as filtration conditions are part of the process filtration and are in the batch record.
1763-1765	We suggest removing for SUS the sterility testing requirement "on receipt and use of each unit".	8.124 Assessment of suppliers of disposable systems including sterilization is critical to the selection and use of these systems. For sterile SUS, verification of sterility should be performed as part of the supplier qualification ~~and on receipt and use of each unit~~. **and verification of the packaging**	Packaging verification will give the information as the products will follow a validated sterilisation process. Packaging integrity indicators could be required
1813-1814	We suggest replacing batch certification by batch release.	9.3 The information from these systems should be used for routine bat~~chcertification~~ **release**	We suggest replacing batch certification by batch release. Certification seems a European concept
1875-1876	We suggest removing batch certification and replacing by product release.	9.13 Results from environmental monitoring should be considered when reviewing batch documentation for finished product batch **ecord review** ~~certification~~ **for product release**	We suggest removing batch certification and replacing by batch release. Certification seems a European concept.
1884-1890	We suggest having consistency between Table 1 and Table 6 for 5µm particles in grade A/B.	.We suggest using Table 1 values in this clause .	5µm values are required for information and trend so no limit should be required. Based on QRM and CCS industry should follow these particle size limits.
1956-1960	For Environmental monitoring we suggest giving the possibility to use automated and rapid microbio methods	9.24 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods (e.g such as settle plates, volumetric air sampling**including rapid and automated microbial monitoring systems**), glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on Grade A and B airflow patterns.	For Environmental monitoring we suggest giving the possibility to use automated and rapid microbio methods.
1962-1965	We suggest aligning sections 9.25 and 9.32.	9.25 Monitoring should include sampling of personnel at periodic intervals during the process. Sampling personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel~~following involvement in~~**after defined** critical	See comments on 9.32
2005-2008	The Note in Table 7 should take into account wording in paragraph 9.4.	9.30 Table 7 Note 1: It should be noted that the types of monitoring methods listed in the table above are examples. **Based on the activities performed not all of the suggested monitoring methods in Table 7 need to be used and other methods may be employed**, provided they meet the intent of providing information across the whole of the critical process where product may be contaminated (e.g. aseptic line set-up, filling and lyophilizer loading), and the different risks inherent in the lower grade zones (C and D).	The Note in Table 7 should take into account wording in paragraph 9.4 where it is suggested that risk assessments (documented in the CCS) "should be performed in order to establish a comprehensive environmental monitoring program, i.e. sampling locations, frequency of monitoring, **monitoring method used** and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions)." Table 7 could read as being prescriptive and require the use of all the suggested monitoring methods, and is not fully aligned with 9.4.
2014-2019	We suggest addind a Note to introduce new microbio technologies.	9.31 Microorganisms detected in Grade A zone and Grade B area should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in Grade C and D areas (for example where action limits or alert levels are exceeded or where atypical or potentially objectionable microorganisms are recovered). The approach to organism identification and investigation should be documented. Note: **Application of newer technologies, based on growth-independent microbial detection**	We suggest addind a Note to introduce new microbio technologies and new technologies, based on growth-independent microbial detection methods. These allow instantaneous detection of a microbial contamination events (e.g. immediate stop of the production followed by separation and reject of potentially contaminated units). This advantage of immediate, appropriate counteraction may outweigh the possibility for microbial identification.
2066-2085	The definition of APS needs to be clarified for APS and Lyophilisation.	9.35 vi The process simulation procedure for lyophilized products should represent the entire aseptic processing chain including filling, transport, loading, chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters**If scientifically justified, process simulation prodedures could be aapplied to individal operations within an entire aseptic processing chain.**	We suggest clarifying the clause to allow consideration of aseptic process simultation to individual operations within a full lyophilisation process as an alternative to applying APS to full length of the lyophilisation process. Such approaches should be scientifically justified.

2093-2095	We suggest removing for corrective action the word "frequently".	9.36 ii. Corrective interventions, that occur ~~frequently~~ during routine production, in a representative number and with the highest degree of acceptable intrusion (e.g. correcting jammed stoppers).	We suggest removing for corrective action the word "frequently", which is not related to corrective actions.
2146-2154	We suggest removing reference to CCS.	9.38 xii. Where campaign manufacturing occurs, such as in the use of Barrier Technologies or manufacture of sterile active substances, consideration should be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk. The performance of "end of production or campaign APS" may be used as additional assurance or investigative purposes; however, their use should be justified ~~in the CCS~~ and should not replace routine APS. If used, it should be demonstrated that any residual product does not negatively impact the recovery of any potential microbial contamination	We suggest removing reference to CCS which is mandatory for whole document as introduced in chapter 2 principle.
2191-2194	This clause should be clarified - we cannot find a way to make a proposal.	9.44 Where processes have materials that contact the product contact surfaces but are then discarded, the discarded material should be simulated with nutrient media and be incubated as part of the APS, unless it can be clearly demonstrated that this waste process would not impact the sterility of the product.	We do not have clear understanding of this clause and we suggest removing it or clarifying to which discarded materials this applies. For instance are the discarded materials stopper bags, or samples dicarded at the beginning of a batch of product. or sterile API or sterile excipients which cannot be filtered.
2225-2227	We suugest removing the number of batches required.	9.48…. iii. A sufficient number of successful, consecutive repeat media fills ~~(normally a minimum of 3)~~ should be conducted in order to demonstrate that the process has been returned to a state of control.	We suggest removing the number of batches required in bracket. Number of repeated APS should be based on QRM and CCS.
2322-2328	We suggest limiting environmental monitoring to Grade A/B areas	10.10 Environmental monitoring data from the **Grade A / B areas** ~~classified~~ areas should be reviewed as part of product batch certification. A written plan should be available that describes the actions to be taken when data from environmental monitoring are found out of trend or exceeding the established limits. For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the ~~certification~~ **batch release** should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid monitoing systems.	We suggest limiting EM to Grade A/B areas. As mentioned several times, we suggest relacing certification by batch release .
2.4	**Glossary:**		
2350	We suugest adding a definition of Air Velocity	**Air Velocity is th measurment of air speed in laminar air fllow.**	Velocity = Unidirectionaal flow speed Velocity measurement is not generally a meaningful parameter in non-unidirectional flow cleanrooms. However, face velocity or airflow are a means for verifying that filters are performing within the design or manufacturer's recommended operating range.
2381	Term not defined - Campaign manufacture	"Campaign manufacture - a separation in time of production. That is, manufacturing a series of batches of the same product in sequence in a given period of time and/or maximum number of batches followed by an appropriate (validated) cleaning procedure."	
2382	Bracketing needs to be defined	A suggested definition of "Bracketing"could be extracted from Annex 15 "A science and risk based validation approach such that only batches on the extremes of certain predetermined and justified design factors, e.g. strength, batch size and/or pack size, are tested during processsimulation. The design assumes that simulation of any intermediate levels is represented by simulation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition, . Bracketing can be applied to different container sizes or different fills in the same container closure system."	We suggest incorporating bracketting definition as it appear in some clauses.
2438	"Critical intervention – An intervention (corrective or inherent) into the critical zone" is considered too restrictive.	"Critical intervention – A direct intervention (corrective or inherent) of the operator into the critical zone without usage of RABS- /isolator gloves or without physical protection by the barrier system"	This needs clarification. This would mean that any intervention, with or without barrier, with or without gloves would fall under this definition.
2439	Cross Contamination	**Accidental transfer of one product to another product should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks.**	We suggest incorporating Cross contamination definition as it is mentioned in some clauses. This clarification is required as Annex 1 addresses Microbio and endotoxin contamination. Chemical and product contamination remain within the Part I of GMP's (General GMP's)
2439	Critical Operations	Operations taking place in the process critical zone	This term appears in the clauses and should be defined as there is critical intervention definition.
2463	Term not defined - Environmental Monitoring Programme	Environmental Monitoring Program - Defined documented programme which describes the routine particulate and microbiological monitoring of processing and manufacturing areas, and includes a corrective action plan when action levels are exceeded.	Use definition of Environmental Monitoring Program from the PIC/S Recommendation on Validation of Aseptic Processing; document number PI 007-14, 1 January 2011.
2497-2500	We suggest improving the definition of isokinetic probes	Isokinetic sampling head –A sampling head designed to disturb the air as little as possible ~~so~~ such that the same particulates go into the nozzle as would have passed the area if the nozzle had it not been there. ~~i.e. the sampling condition in which the mean velocity of the air entering the sample probe inlet is nearly the same (± 20 percent) as the mean velocity of the airflow at that location.~~	The example provided is too limiting, it does not allow for any corrections or other approaches. It also does not account for anisokinetic sampling tolerances based upon the 0.5um and 5.0um sampling errors. It can be shown that an 'ideal' scenario where flow rate is unidirectional at 0.45m/s being sampled by a 28.3 l/min (1 CFM) instrument can have allowable differences in inlet diameter sizes. The associated errors are supported by the work described in FS209E (1992) and the anisokinetic error is based upon the experimental work of Belyaev and Levin (1972, 1974). **Probe Diameter** / **Comment** / **Anisokinetic correction (see formula below)** **36.53mm** / **Ideal size for isokinetic sampling** / **NONE** **50mm** / **The larger size inlet is therefore likely to over-sample particles being measured.** / **0.5um correction = 1.038** **5.0um correction = 1.163** **Therefore an 11% reduction associated with the 5.0um particles needs to be applied** **20mm** / **The smaller inlet is likely to under-sample particles being measured, it may also move free particle trajectory due to increased inlet velocity** / **0.5um correction = 0.997** **5.0um correction = 0.824** **Therefore an 18% increase associated with the 5.0um particles needs to be applied** **20mm - 41mm** / **Range of probe diameters requiring no change to values based on anisokinetic sampling.** / **NONE** Formula for anisokinetic sampling Belyaev and Levin 
2474	We suggest incorporating a definition for Gloveless isolator	Gloveless isolators: closed isolators using robotics and which do not need operator intervention through	
2534	The term non viable is used when referring to particle counts we suggest using Total Particules instead of non viable particules.	Total Particles: represent all the particles sampled for monitoring purpose in clean rooms. Viable + non viable	The equipment used to count particles cannot determine if they are viable or non viable.
2544	Glossary: Raw material – Any ingredient intended for use in the manufacture of a sterile product, including those that may not appear in the final drug product.	We suggest replacing "raw material" by 'component"	Replace the term "raw material" with "component" (as used by FDA) or "starting material" (from Glossary to Eurdalex vol. 4) throughout the document The definition of "Component" in 21CFR210.03 is identical to the definition of "Raw material" in draft Annex 1, which is confusing.
	The term "ancillary item" is used several times throughout the document but not defined. By including this definition, misunderstandings should be avoided.		
2564	We suggest adding a definitinon for "significant intervention"		"Significant intervention" is quoted in 10.6 clause and there is the possibility of misunterpretation with "critical intervention"
2610	Term not defined - Z Value		D Value is defined, Z value is mentioned but not defined