European Commission

Canny 康利华咨询
A Tigermed Company

欧盟GMP附录1无菌药品更新对比（全文）

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梳理

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欧盟 GMP 附录 1 无菌药品更新对比

欧盟无菌附录 1971 年首次颁布，现行版是 2008 版。EMA 于 2017 年发布第一次征求意见稿，修订幅度非常大，基本上属于重写而不仅仅是修订，征求意见稿发布后收到了各相关方的反馈逾 6000 条。2020 年 2 月发布第二轮征求意见稿。2022 年 8 月 22 日最终版定稿，8 月 25 日公开发布。

定稿指南要求的最后实施期限是 2023 年 8 月 25 日，指南中的第 8.123 条的最后实施期限为 2024 年 8 月 25 日。

8.123 冻干机和相关产品转移和装载/卸载区域应经过设计，尽可能减少操作人员的干预。冻干机灭菌的频率应根据设计和使用过程中与系统污染相关的风险来进行确定。没有屏障技术隔离的手动装载或卸载的冻干机应在每次装载前进行灭菌。对于通过自动化系统装载和卸载或由密闭的屏障系统保护的冻干机，应进行论证并记录其灭菌频率，并作为 CCS 的组成部分。

与第二版征求意见稿相比，正式版保留了基本架构，目录对比如下：

1st	2nd	Final-20220825		Current Annex 1-2008
		章节	条目数	
1. Scope	1. Scope	1. Scope	三段	N/A
2. Principle	2. Principle	2. Principle	7 条	Principle
3.Pharmaceutical Quality System (PQS)	3.Pharmaceutical Quality System (PQS)	3. Pharmaceutical Quality System (PQS)	2 条	N/A
4. Personnel	4. Premises	4. Premises • Barrier Technologies • Cleanroom and clean air equipment qualification • Disinfection	36 条	• Premises • Clean room and clean air device classification • Isolator technology • Sanitation
5. Premises	5. Equipment	5. Equipment	9 条	Equipment
6. Equipment	6. Utilities	6. Utilities • Water systems • Steam used as a direct sterilising agent • Gases and vacuum systems • Heating and cooling and hydraulic systems	22 条	N/A
7. Utilities	7. Personnel	7. Personnel	18 条	Personnel

1st	2nd	Final-20220825		Current Annex 1-2008
		章节	条目数	
8. Production and specific technologies	8. Production and specific technologies	8. Production and specific technologies ♦ Terminally sterilised products ♦ Aseptic preparation and processing ♦ Finishing of sterile products ♦ Sterilisation ♦ Sterilisation by heat ♦ Moist heat sterilization ♦ Dry heat sterilization ♦ Sterilisation by radiation ♦ Sterilisation with ethylene oxide ♦ Filter sterilisation of products which cannot be sterilised in their final container ♦ Form-Fill-Seal (FFS) ♦ Blow-Fill-Seal ♦ Lyophilization ♦ Closed systems ♦ Single use systems (SUS)	139 条	♦ Blow/fill/seal technology ♦ Terminally sterilised products ♦ Aseptic preparation ♦ Processing ♦ Sterilisation ♦ Sterilisation by heat ♦ Moist heat ♦ Dry heat ♦ Sterilisation by radiation ♦ Sterilisation with ethylene oxide ♦ Filtration of medicinal products which cannot be sterilised in their final container ♦ Finishing of sterile products
9. Viable and non-viable environmental and process monitoring	9. Viable and non-viable environmental and process monitoring	9. Environmental and process monitoring ♦ General ♦ Environmental and process monitoring ♦ Environmental monitoring – total particle ♦ Environmental and personnel monitoring – viable particle ♦ Aseptic process simulation (APS) (also known as media fill)	49 条	♦ Clean room and clean air device classification ♦ Clean room and clean air device monitoring ♦ Processing
10. Quality control (QC)	10. Quality control (QC)	10. Quality control (QC)	11 条	Quality control
11. Glossary	11. Glossary	11. Glossary	N/A	N/A

注：现行版无菌附录没有明显的章节；征求意见稿以及此次的修订版分章节论述了无菌生产的相关各项要求。

1-11 章内容差异的简要对比（详情参见附件）

正式版章节	与第二版征求意见稿相比的主要变化	与 2008 版相比的主要变化	2008 版的相关条目
分为 11 个章节	基本结构未变	现行版无菌附录没有明显的章节；此次的修订版分章节论述了无菌生产的相关各项要求	N/A
1. Scope	♦ 在 pyrogen 的基础上增加了 endotoxin。 ♦ 对指南应用的范围在征求意见稿的基础上扩展增加了厂房、设备、系统的设计和控制。	N/A	N/A
2. Principle	♦ 调整了用词。 ♦ 增加了对原材料和包装材料的控制原则，要求对其进行适当的控制和检验，确保与用途相适应的生物荷载以及内毒素/热原水平。 ♦ 强调了 CCS 应纳入周期性管理评审以及与体系的关联交互。 ♦ CCS 中的 Process risk assessment 改为 Process risk management ♦ CCS 中增加了灭菌工艺验证以及对根本原因的确定。	现行版强调了颗粒、微生物以及热原污染防控、人员和质量保证的重要性，强调了不能仅依靠检查结果确保无菌和其他质量特性，但没有做具体陈述。本版细化了无菌保证的基本原则，最为显著的变化是增加了关于污染控制策略（CCS）的要求。	Principle，71，82
3. Pharmaceutical Quality System (PQS)	♦ 调整了用词。 ♦ 强调了高层在质量体系中的作用。	增加了专门的质量体系管理的内容，此章节应结合 Chapter 1 of the GMP guidelines (Part I - Basic Requirements for Medicinal Products)一并阅读和理解运用。	N/A
4. Premises	♦ 调整了用词。 ♦ 不建议在洁净区使用推拉门。 ♦ 强调洁净室的建筑材料和用品应能经受反复的清洗和消毒操作，包括杀孢子剂的使用。 ♦ 调整了隔离器和 RABs 的设计、背景要求、手套系统等描述。	♦ 将原先分散的各类要求汇总到统一的章节进行了详细的论述和要求。例如 – 增加了单向流可视化研究的要求； – 细化了隔离器和 RABs 的要求； – 细分了洁净室分级和确认的要求； – 明确了洁净室分级应当在模拟操作期间进行； ♦ 调整了个别的标准。例如 – 压差指导值由 10-15pa 改为最低 10pa； – 洁净室空气标准进行了微调； – 自净（clean-up）时间的指导值由 15-20min 改为不低于 15min； – A 级微生物监测标准由小于 1 改为不得生长。	1，2，3，4，5，7，14，16，19，21，22，23，24，25，46，47，48，49，50，51，52，53，54，55，61，62，63，75，81

正式版章节	与第二版征求意见稿相比的主要变化	与 2008 版相比的主要变化	2008 版的相关条目
5. Equipment	♦ 调整了用词。 ♦ 删去了粒子监测软管弯曲半径的要求。 ♦ 细化了无菌操作工艺中，直接接触与间接接触部件的要求。	♦ 增加了无菌操作工艺中，直接接触与间接接触部件的要求。 ♦ 明确了粒子计数器和取样管需要确认。细化了取样管的要求。	6，11，56，57，58，60
6. Utilities	♦ 调整了用词。 ♦ 增加了水系统流速应进行确认并日常监测。 ♦ 增加了水系统消毒/再生后水质检测的要求。 ♦ 细化了水系统监测持续监测的要求，例如警戒水平的制定与评估、取样计划原则。	♦ 增加了对公用系统的管理性要求并应纳入 CCS。 ♦ 细化了对图纸和有关记录的细节要求，例如明确要求了管道流向、坡度、取样点等信息。 ♦ 明确了高风险系统的基本定义。并要求对高风险系统的关键参数和关键质量属性进行趋势分析。 ♦ 增加了水系统监测持续监测的要求，例如警戒水平的制定与评估、取样计划原则。 ♦ 增加了水系统消毒/再生后水质检测的要求。 ♦ 细化了对水系统的要求。例如湍流保持和流速的确认和监测、注射用水系统的在线监测配置等等。引入了非蒸馏法制备注射用水的描述。 ♦ 增加了对蒸汽、气体和加热冷却系统更为详细的要求。	49，59，72，96
7. Personnel	♦ 调整了用词。 ♦ 对更衣相关的细节进行了描述。例如更衣前后检查工作服的完整性、洁净服的检测、细化了 B 级区洁净服的要求。尤其强调了袜子的穿戴问题。	♦ 增加了关于进入 A 级和 B 级区域的人员应接受无菌更衣和无菌行为培训方面的细节要求。 ♦ 增加了对无菌操作人员资格确认的细节要求。 ♦ 增加了对洁净室内可能会使用的便携式电子设备的原则性要求。 ♦ 增加了洁净服完整性检查的细节要求。 ♦ 细化了对洁净服清洗的原则性要求。 ♦ 细化了 B 级区洁净服的要求。尤其强调了袜子的穿戴问题。 ♦ 增加了对手套定期消毒和更换的要求。 ♦ 强调了无菌操作人员要始终遵循无菌操作技术，以及可视化研究的回顾应作为培训计划的一部分。	36，37，38，39，40，41，42，43，44，45，73
8. Production and specific technologies	♦ 调整用词。 ♦ 除因增删导致的序号变化外，还调整了部分条款的先后次序，例如原“8.7 Aseptic preparation and processing”调整至术语	♦ 增加了大量的关于生产和无菌技术、生产技术的细节性要求。例如： – 增加了 FFS 的要求。 – 细化了 BFS 的要求。	17，26，27，28，29，30，31，32，33，34，35，64，65，76，77，78，

正式版章节	与第二版征求意见稿相比的主要变化	与 2008 版相比的主要变化	2008 版的相关条目
	部分；原 8.60 调整为 8.56 等。 ♦ 恢复了个别条款并调整次序。例如恢复了原已删除的第一版征求意见稿中的 8.42 并调整至正式版的 4.11。 ♦ 细化了对干预活动的要求。 ♦ 细化了包装完整性测试的要求。 ♦ 增加了灭菌验证中被评估为最差情况的装载应当至少每年进行再验证，其他情形的装载可根据 CCS 中的评估进行。 ♦ 细化了热力灭菌中探头配置有关的描述。 ♦ 增加了湿热灭菌后物品应干燥及检查的要求。 ♦ 干热灭菌/除热原验证装载配置强调了最大和最小装载。 ♦ 调整了 FFS 和 BFS 部分的描述，增加了污染控制、关键参数、环境以及维护的要求。 ♦ 增加了对冻干产品转移和进出料系统的消毒要求。（8.123）	– 细化了对 RABs 和隔离器的要求。 – 增加并细化了对干预活动的要求。 – 细化了包装完整性测试的要求。 – 增加和细化了灭菌方面的要求，包括灭菌参数和灭菌程序设计和标准等方面的内容。 – 增加了对冻干产品转移和进出料系统的消毒要求。（8.123） – 归纳总结了原现行版 31-35 条对环境配置的要求。 – 增加并细化了对灯检缺陷检查的要求，例如缺陷库的建立、缺陷分类、趋势分析等要求。 – 增加了灭菌方法设计的原则性要求。 – 强调了最大和最小装载的验证应当是整体灭菌验证策略的组成部分。 – 增加了灭菌验证中被评估为最差情况的装载应当至少每年进行再验证，其他情形的装载可根据 CCS 中的评估进行。 – 增加了对物料、组件、设备灭菌的一些细节操作要求。 – 增加了过滤系统设计的考量要求、验证要求、监测要求、在线完整性测试等方面的内容。 – 增加了一次性使用系统的要求。 ♦ 删除了辐照灭菌中的大量描述，相关的细节内容描述为参见“Annex 12 Use of Ionising Radiation in the Manufacture of Medicinal Products”。	79，81，83，84，85，86，87，88，89，90，91，92，93，94，95，97，98，99，100，101，102，103，104，105，106，107，108，109，110，111，112，113，114，115，116，117，118，119，120，121，122，123，124
9. Environmental and process monitoring	♦ 调整了用词。 ♦ 调整了描述次序，例如原 9.32 和 9.33 调整至 9.25，9.26，9.27. ♦ 监测要素增加了温湿度及其他。 ♦ 对建立监测计划的目的进行了描述。 ♦ 明确监测位置应当通过风险评估确定，简述了风险。 ♦ 警戒限和纠偏限原则上参考本章的表格，但也允许根据需要制定更严格的标准。 ♦ 强调了趋势分析应特别注意那些表示洁净	♦ 增加了环境监测的原则性要求，例如建立监测计划的目的、监测要素、监测位置应当通过风险评估确定等。 ♦ 增加了监测程序的要求。 ♦ 增加细化了监测限度、趋势分析等方面的要求。 ♦ 增加细化了对微生物监测的要求，例如关键干预和每次退出 B 级区对人员采样的要求、所发现微生物鉴别的要求。 ♦ 细化了 APS 的要求。例如 – 增加了 APS 的作用，强调了应通过工艺设计、PQS、培训等实现无菌保证，而不是仅依赖 APS。 – 描述了 APS 的模拟范围和考虑因素。	8，9，10，11，12，13，15，18，19，20，66，67，68，69，70

正式版章节	与第二版征求意见稿相比的主要变化	与 2008 版相比的主要变化	2008 版的相关条目
	度恶化或失控时所采集到的微生物或难以控制的微生物，例如形成孢子的微生物。 ♦ 增加了发现有≥5μm 的大粒子时调查的要求。 ♦ 增加细化了对微生物监测的要求，例如关键干预和每次退出 B 级区对人员采样的要求、所发现微生物鉴别的要求。 ♦ 细化了 APS 的要求。	– 增加了对干预的考虑要点。 – 增加了制定 APS 计划时需要考虑的要点。 – 增加了对无菌活性成分进行 APS 时的原则性要求。 – 增加了对手工无菌操作情况下的 APS 的要求。 – 增加了灌装后的操作要求，例如翻转、倒置等，以及容器剔废的原则。 – 细化了培养和观察的原则要求。 – 细化了调查和后续采取措施的要求。 ♦ 增加了 APS 记录以及重新启动初始验证的要求。	
10. Quality control (QC) 质量控制（QC）	♦ 调整了用词。 ♦ 增加了对培养基控制的要求。	♦ 增加了必要时原料、成分等应对微生物和热原/内毒素进行控制的要求。 ♦ 增加了关于无菌检查与放行的一些要求。 ♦ 增加了对培养基控制的要求。 ♦ 增加了洁净区的环境监测数据和趋势应作为产品批次放行的一部分进行审核的要求。 ♦ 增加了使用快速测定方法时应验证的要求。	74，80，125，126，127
11. Glossary	现行版的没有词汇表，无对比内容		N/A

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说明：

When transfer	表示正式版删去的内容
change rooms	表示正式版与第二版征求意见不同的内容
appropriate cleanrooms	表示第二版征求意见稿增加的内容
~~clean areas~~	表示第二版征求意见稿中删去的第一版征求意见稿的内容
General	表示当前版（2008 年版）无菌附录中的分节

EU GMP ANNEX 1 1. Scope

2nd VS 1st	Final-20220825	Current Annex 1-2008
The manufacture of sterile ~~medicinal~~ products covers a wide range of sterile product types~~, (sterile~~ (active substance ~~through to~~ , sterile excipient, primary packaging material and finished dosage form), ~~batch~~ packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes~~), primary packaging materials~~) and technologies (e.g. Biotechnology, classical small molecule manufacturing and closed systems). This Annex provides general guidance that should be used for the manufacture of all sterile ~~medicinal~~ products ~~and sterile active substances, via adaption,~~ using the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and pyrogen contamination ~~associated with microbes~~ is prevented in the final product.	The manufacture of sterile products covers a wide range of sterile product types (active substance, excipient, primary packaging material and finished dosage form), packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes) and technologies (e.g. biotechnology, classical small molecule manufacturing systems and closed systems). This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.	N/A
QRM applies to this document in its entirety and will not be referred to in specific paragraphs. Where specific limits or frequencies are written, these should be considered as a minimum requirement. They are stated due to regulatory historical experience of issues that have previously been identified and have impacted the safety of patients.	QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs. Where specific limits or frequencies or ranges are specified, these should be considered as a minimum requirement. They are stated due to historical regulatory experience of issues that have been identified and have impacted the safety of patients.	N/A
The intent of the Annex is to provide guidance for the manufacture of sterile ~~medicinal~~ products. However some of the principles and guidance, such as contamination control strategy, ~~room qualification~~ design of premises, cleanroom classification, qualification, monitoring and personnel gowning, may be used to support the	The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of	N/A

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manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates but where the control and reduction of microbial, particulate and pyrogen contamination~~, to reduce it as far as possible,~~ is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.	other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.	

EU GMP ANNEX 1 **2. Principle**

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2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of ~~microbiological~~ microbial, particulate and pyrogen contamination. The following key areas should be considered: ~~a)~~ i. Facility, equipment and process design ~~must~~ should be optimized, qualified and validated according to ~~Annex 11 and Annex15~~the relevant sections of ~~EU~~ the Good Manufacturing Practices (GMP) guide. The use of appropriate ~~current~~ technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid microbial testing and monitoring systems) should be ~~implemented~~ considered to ~~ensure~~ increase the protection ~~and control~~ of the product from potential extraneous sources of particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants	2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered: i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guidelines. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.	**Principle** The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test. **Processing** 82. The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on

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in the environment and product. ~~b)~~ ii. Personnel ~~must~~ should have ~~appropriate skills~~ adequate qualifications and experience, training and ~~attitudes~~ attitude with a specific focus on the principles involved in the protection of sterile product during the manufacturing, packaging and distribution processes. ~~c)~~ iii. Processes and monitoring systems for sterile product manufacture ~~must~~ should be designed, commissioned, qualified and monitored by personnel with appropriate process, engineering and microbiological knowledge.	ii. Personnel should have adequate qualifications and experience, training and behaviour with a specific focus on the principles involved in the protection of sterile product during the manufacturing, packaging and distribution processes. iii. Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified, monitored and regularly reviewed by personnel with appropriate process, engineering and microbiological knowledge. iv. Raw materials and packaging materials should be adequately controlled and tested to ensure that level of bioburden and endotoxin/pyrogen are suitable for use.	performance history or when any significant change is made in the process or equipment.
2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles ~~that~~ to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. ~~Risk assessments should be used to justify~~ Where alternative approaches ~~to those specified in this Annex only if~~ are used, these ~~alternative~~ should be ~~approaches~~ supported by appropriate rationales and risk assessment and should meet ~~or surpass~~ the intent of this Annex. QRM priorities should include good design of the facility, equipment and process in the first instance, then implementation of well-designed procedures, with monitoring systems as the final element that demonstrate that the design and procedures have been correctly implemented and continue to perform in line	2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale, risk assessment and mitigation, and should meet the intent of this Annex. In the first instance, QRM priorities should include appropriate design of the facility, equipment and processes, followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility.	Processing 71. Care should be taken that any validation does not compromise the processes.

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with expectations. Exclusively monitoring or testing does not give assurance of sterility.		
2.3 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 (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed~~. This assessment~~ to manage risks associated with contamination. The CCS should ~~lead to corrective~~ be actively updated and ~~preventative actions being taken as necessary. The strategy~~ should ~~consider all aspects of contamination control and its life cycle with~~drive continuous improvement of the manufacturing ~~ongoing and periodic review and update of the strategy as appropriate.~~ and control methods.	2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.	N/A
2.4 Contamination control and steps taken to ~~minimize~~ minimize the risk of contamination from microbial and particulate sources are a series of successively linked events ~~or~~ and measures. These are typically assessed, controlled and monitored individually but ~~these many sources~~ their collective effectiveness should be considered ~~holistically.~~ altogether.	2.4 Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.	N/A
2.5 The development of ~~such strategies~~ the CCS requires thorough technical and process knowledge. Potential sources of contamination are attributable to ~~microbiological~~ microbial and cellular debris (e.g. ~~pyrogens/~~ pyrogen, endotoxins) as well as particulate	2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles).	N/A

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matter (e.g. glass and other visible and sub-visible particulates).~~particles).~~ Elements to be considered within ~~such~~ a documented ~~contamination control strategy~~ CCS should include (but are not ~~be~~ limited to): ~~a)~~i. Design of both the plant and ~~process~~ processes ~~b)~~ii. ~~Equipment~~ Premises and ~~facilities~~ equipment. ~~c)~~iv. Personnel. ~~d)~~v. Utilities. ~~e)~~vi. Raw ~~Materials Control~~ material controls – including in-process controls. ~~f)~~vii. Product containers and closures. ~~g)~~viii. Vendor approval – such as key component suppliers, sterilization of components and single use systems (SUS), and services. ~~h)~~ix. For outsourced services, such as sterilization, sufficient evidence should be provided to the contract giver to ensure the process is operating correctly. ~~i)~~x. Process risk assessment. ~~j)~~xi. Process validation. ~~k)~~xii. Preventative maintenance – maintaining equipment, utilities and premises (planned and	Elements to be considered within a CCS should include (but are not limited to): i. Design of both the plant and processes including the associated documentation. ii. Premises and equipment. iii. Personnel. iv. Utilities. v. Raw material controls – including in-process controls. vi. Product containers and closures. vii. Vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers. viii. Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services. ix. Process risk management. x. Process validation. xi. Validation of sterilisation processes. xii. Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned	

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unplanned maintenance) to a standard that will not add significant risk of contamination. ~~l)~~xiii. Cleaning and disinfection. ~~m)~~xiv. Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, modern methods that optimize the detection of environmental contamination. ~~n)~~xv. Prevention – trending, investigation, corrective and preventive actions (CAPA), root cause determination and the need for more ~~robust~~ comprehensive investigational tools. xvi. Continuous improvement based on information derived from the above ~~systems~~.	maintenance) to a standard that will ensure there is no additional risk of contamination. xiii. Cleaning and disinfection. xiv. Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination. xv. Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools. xvi. Continuous improvement based on information derived from the above.	
2.6 The CCS should consider all aspects of contamination control and its life cycle with ongoing and periodic review resulting in updates within the quality system as appropriate.	2.6 The CCS should consider all aspects of contamination control with ongoing and periodic review resulting in updates within the pharmaceutical quality system as appropriate. Changes to the systems in place should be assessed for any impact on the CCS before and after implementation.	N/A
2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should ~~must~~ not be placed on any terminal process or finished product test.	2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test.	Principle The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of

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		manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.
~~Note 1:~~ ~~This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces etc. Reference should be made to other documents such as the EN/ISO Standards and Pharmacopoeial monographs for more detailed guidance.~~	N/A	Note: This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces etc. Reference should be made to other documents such as the EN/ISO Standards.
~~Note 2:~~ ~~Where national legislation permits, additional guidance regarding the preparation of unlicensed sterile medicinal products normally performed by healthcare establishments for direct supply to patients, reference may be made to the Annex 1: "Guidelines on the standards required for the sterile preparation of medicinal products" of the PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments, PE 010.~~	N/A	N/A

EU GMP ANNEX 1 3. Pharmaceutical Quality System (PQS)

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3.1 The manufacture of sterile ~~medicinal~~ products is a complex activity that requires ~~additional~~ specific controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's ~~Pharmaceutical Quality System (~~PQS~~)~~ should	3.1 The manufacture of sterile products is a complex activity that requires specific controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's PQS should encompass and address the	N/A

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encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that ~~all final products are free from microbial and other contamination~~ microbial, particulate and pyrogen contamination is minimized in sterile products. In addition to the PQS requirements detailed in Chapter 1 of the ~~EU~~ GMPs, the PQS for sterile product manufacture~~s~~ should also ensure that: ~~a)~~ i. ~~There is an~~ An effective risk management system is integrated into all areas of the product life cycle with the aim to minimize microbial contamination and to ensure the ~~safety,~~ quality ~~and efficacy~~ of sterile ~~manufactured~~ products manufactured~~, including assurance of sterility~~. ~~b)~~ ii. The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that have an impact on product quality. ~~c)~~ iii. Root cause analysis of procedural, process or equipment failure is ~~key to ensure~~ performed in such a way that the risk to product is correctly understood and suitable corrective and preventative actions (CAPA) are implemented. ~~d)~~ iv. Risk management is ~~performed~~ applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks ~~to prevent contamination, to monitor and detect contamination, and to establish process requirements and acceptance criteria for all elements of a sterile manufacturing process~~. ~~The risk~~ Risk management should be documented and should include the rationale for decisions taken in relation	specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that the risk of microbial, particulate and endotoxin/pyrogen contamination is minimized in sterile products. In addition to the PQS requirements detailed in Chapter 1 of the GMP guidelines (Part I - Basic Requirements for Medicinal Products), the PQS for sterile product manufacture should also ensure that: i. An effective risk management system is integrated into all areas of the product life cycle with the aim to minimize microbial contamination and to ensure the quality of sterile products manufactured. ii. The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that have an impact on product quality. iii. Root cause analysis of procedural, process or equipment failure is performed in such a way that the risk to product is correctly identified and understood so that suitable corrective and preventive actions (CAPA) are implemented. iv. Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.	

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to ~~mitigating risks, discounting of potential risks~~ risk reduction and acceptance of residual risk. v. The risk ~~assessment~~ management outcome should be reviewed regularly as part of on-going quality management, during change control and during the periodic product quality review. ~~e)~~ vi. Processes associated with the finishing and transport of sterile products should not compromise the ~~finished~~ sterile product ~~in terms of~~. Aspects that should be considered include: container integrity, ~~or pose a~~ risks of contamination and avoidance of degradation by ~~ensure~~ ensuring that ~~medicinal~~ products are stored and maintained in accordance with the registered storage conditions. ~~f)~~ vii. Persons responsible for the quality release of sterile ~~medicines~~ products ~~should~~ have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile ~~dosage forms~~ products and their critical quality attributes. This is in order to ~~be able to~~ allow such persons to ascertain that the ~~medicines~~ sterile products have been manufactured in accordance with the registered specifications and are of the required ~~safety,~~ quality ~~and efficacy~~.	v. Senior management should effectively oversee the state of control throughout the facility and product lifecycle. Risk management outcome should be reviewed regularly as part of the on-going quality management, during change, in the event of a significant emerging problem, and during the periodic product quality review. vi. Processes associated with the finishing, storage and transport of sterile products should not compromise the sterile product. Aspects that should be considered include: container integrity, risks of contamination and avoidance of degradation by ensuring that products are stored and maintained in accordance with the registered storage conditions. vii. Persons responsible for the certification/release of sterile products have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile products and the associated critical quality attributes. This is in order to allow such persons to determine if the sterile products have been manufactured in accordance with the registered specifications and approved process and are of the required quality.	
3.2 ~~Investigations should be performed into~~ All non-conformities, such as sterility test failures ~~or~~, environmental monitoring excursions or deviations from established procedures should be investigated. ~~, with a specific focus regarding~~ The investigation should determine the potential impact ~~to sterility, to not only the~~	3.2 All non-conformities, such as sterility test failures, environmental monitoring excursions or deviations from established procedures should be adequately investigated before certification/release of the batch. The investigation should determine the potential impact upon process and	N/A

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~~specific batch concerned but also~~ upon process and product quality and whether any other processes or batches are potentially impacted ~~batch~~. The reason~~s~~ for including or excluding a product or batch from the scope of the investigation should be clearly ~~recorded and~~ justified and recorded ~~within the investigation~~.	product quality and whether any other processes or batches are potentially impacted. The reason for including or excluding a product or batch from the scope of the investigation should be clearly justified and recorded.	

EU GMP ANNEX 1 4. Premises

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~~5.1~~4.1 The manufacture of sterile products should be carried out in ~~clean areas~~ appropriate cleanrooms, entry to which should be through changing rooms that act as airlocks for personnel and ~~/or~~ airlocks for equipment and materials. ~~Clean areas~~ Cleanrooms should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and capable of evaluating the state of environmental conditions for cleanrooms, airlocks and pass-throughs used for material and equipment transfer.	4.1 The manufacture of sterile products should be carried out in appropriate cleanrooms, entry to which should be through change rooms that act as airlocks for personnel and airlocks for equipment and materials. Cleanrooms and change rooms should be maintained to an appropriate cleanliness standard and supplied with air that has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.	**General** 1. The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.
~~5.2~~4.2 The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within ~~the clean area~~ the cleanroom or facility to prevent mix up and contamination.	4.2 The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix up and contamination.	**General** 2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.
4.3 Restricted Access Barrier Systems (RABS) and isolators are beneficial in assuring the required conditions and minimizing the microbial contamination associated	4.3 Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct	N/A

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with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.	human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.	
~~5.3~~4.4 For the manufacture of sterile ~~medicinal~~ products ~~4 grades of clean room can be distinguished.~~ there are four grades of cleanroom.	4.4 For the manufacture of sterile products, there are four grades of cleanroom/zone.	**General** 3 For the manufacture of sterile medicinal products 4 grades can be distinguished.
Grade A: The ~~local~~ critical zone for high risk operations or for making aseptic connections by ensuring protection by first air, (e.g. aseptic processing line, filling zone, stopper bowl~~s~~, open ampoules and vials,) ~~making aseptic connections.~~ Normally, such conditions are provided by a localised air flow protection, such as ~~laminar~~ unidirectional air flow work stations, RABS 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. During initial qualification and requalification air speeds may be measured either close to the terminal air filter face or at the working height, Where ever the measurement is taken it is important to note that the key objective is to ensure that air visualization studies should correlate with the airspeed measurement to demonstrate air movement that supports protection of the product and open components with unidirectional air at the working height, where high risk operations and product and components are exposed.~~ The maintenance of unidirectional airflow should be demonstrated and validated across the whole of the grade A area. ~~Entry~~ Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A ~~area~~ zone by operators should be minimized by	Grade A: The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.	Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.

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~~facility~~ premises, equipment, process and procedural design.		
Grade B: For aseptic preparation and filling, this is the background ~~environment~~ cleanroom for the grade A zone （where is not an isolator）. When transfer holes are used to transfer filled, closed products to an adjacent cleanroom~~s~~ of a lower grade, airflow visualization studies should demonstrate that air dose not ingress from the lower grade cleanrooms to the grade B. Pressure differentials should be continuously monitored ~~In general, only grade C cleanrooms should interface with the grade B aseptic processing area.~~ Cleanrooms of Lower grades than grade B can be considered where isolator technology is used (refer to clause 4.22).	Grade B: For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Air pressure differences should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used (see paragraph 4.20).	Grade B: For aseptic preparation and filling, this is the background environment for the grade A zone.
Grade C and D: ~~Clean areas~~ 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).	Grade C and D: These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation/filling of terminally sterilised products. (See section 8 for the specific details on terminal sterilisation activities).	Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.
~~5.4~~4.5 In ~~clean areas~~ cleanrooms, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of ~~particles~~ particulates or micro-organisms and to permit the repeated application of cleaning, ~~agents, and~~ disinfectants and sporicidal agents where used.	4.5 In cleanrooms and critical zones, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms.	46. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.
~~5.5~~4.6 To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses that are difficult to clean effectively therefore ~~and a minimum of~~ projecting ledges, shelves, cupboards and equipment should be kept to a minimum. Doors should be designed	4.6 To reduce accumulation of dust and to facilitate cleaning there should be no recesses that are difficult to clean effectively, therefore projecting ledges, shelves, cupboards and equipment should be kept to a minimum. Doors should be designed to avoid recesses that cannot be cleaned.	47. To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to

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to avoid ~~uncleanable~~ recesses that cannot be cleaned.	Sliding doors may be undesirable for this reason.	avoid those uncleanable recesses; sliding doors may be undesirable for this reason.
~~5.6~~4.7 Materials ~~liable to generate fibres should not be permitted in clean areas~~ used in cleanrooms should be selected to minimize generation of particle.	4.7 Materials used in cleanrooms, both in the construction of the room and for items used within the room, should be selected to minimize generation of particles and to permit the repeated application of cleaning, disinfectant and sporicidal agents where used.	**Processing** 75. Containers and materials liable to generate fibres should be minimised in clean areas.
~~5.7~~4.8 ~~False~~ Ceilings should be designed and sealed to prevent contamination from the space above them.	4.8 Ceilings should be designed and sealed to prevent contamination from the space above them.	48. False ceilings should be sealed to prevent contamination from the space above them.
N/A 6. Utilities 6.6	N/A 6. Utilities 6.6	49. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.
~~5.8~~4.9 Sinks and drains should be prohibited in grade A zone and Grade ~~A/~~B areas. In other cleanrooms ~~areas~~, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade cleanrooms should be fitted with traps or water seals designed to prevent back flow and should be regularly cleaned ~~and~~, disinfected and maintained.	4.9 Sinks and drains should be prohibited in the grade A and grade B areas. In other cleanrooms, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade cleanrooms should be fitted with traps or water seals designed to prevent back flow and should be regularly cleaned, disinfected and maintained.	50. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent backflow.
4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented.	4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented.	N/A
4.11 The transfer of materials, equipment, and components into an aseptic processing area should be carried out via a unidirectional process. Where possible, items should be sterilized and passed into the area	4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process. Where possible, items should be sterilised and passed into these areas through double-	Processing 81. Components, containers, equipment and any other article required in a clean area where aseptic work takes place

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through double-ended sterilizers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilization on transfer of the items is not possible, a procedure which achieves the same objective of not introducing contaminant should be validated and implemented, (e.g. using an effective transfer disinfection, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter).	ended sterilisers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilisation upon transfer of the items is not possible, a procedure which achieves the same objective of not introducing contamination should be validated and implemented, (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter). The removal of items from the grade A and B areas (e.g. materials, waste, environmental samples) should be carried out via a separate unidirectional process. If this is not possible, time-based separation of movement (incoming/exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.	should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters.
~~5.9~~4.12 Airlocks should be designed and used to provide physical separation and to minimize microbial and particulate contamination of the different areas, and should be present for material and personnel moving ~~from~~ between different grades. Wherever possible, ~~typically~~ airlocks used for personnel movement should be ~~are~~ separated ~~to~~ from those used for material movement. Where this is not practical, time-based separation of movement (personnel /material) by procedure should be considered. Airlocks ~~They~~ should be flushed effectively with filtered air to ensure that the grade of the cleanroom is maintained. The final stage of the airlock should, in the at-rest state, ~~be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is generally desirable.~~ be of the same cleanliness grade (viable and non-viable) as the cleanroom into which it leads. The use of separate changing rooms for entering and leaving Grade B	4.12 Airlocks should be designed and used to provide physical separation and to minimize microbial and particle contamination of the different areas and should be present for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement should be separated from those used for material movement. Where this is not practical, time-based separation of movement (personnel/material) by procedure should be considered. Airlocks should be flushed effectively with filtered air to ensure that the grade of the cleanroom is maintained. The final stage of the airlock should, in the “at rest” state, be of the same cleanliness grade (viable and total particle) as the cleanroom into which it leads. The use of separate change rooms for entering and leaving the grade B area is desirable. Where this is not practical, time-based separation of activities (ingress/egress) by procedure should be considered. Where the CCS indicates that the risk of contamination is high, separate change	51. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.

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cleanrooms is desirable. Where this is not practical, time-based separation of activities (ingress/egress) by procedure should be considered. Where the CCS indicates that the risk of cross-contamination is high, separate changing rooms for entering and leaving production areas should be considered. Airlocks should be designed as follow: i. Personnel airlocks. ~~A cascade concept should be followed for personnel~~ Areas of increasing cleanliness used for entry of personnel (e.g. from grade D to grade C to grade B). In general hand washing facilities should be provided only in the first stage of the changing rooms and not be present in changing rooms directly accessing Grade B cleanrooms. ii. Material airlocks : used for materials and equipment transfer. ● ~~For airlocks leading to grade A and B areas~~, only materials and equipment that have been included ~~as part of the qualification~~ on an approved list, developed during validation of the transfer process, should be allowed to be transferred into the ~~grade A/B area~~ Grade A zone or Grade B cleanroom via ~~the~~ an air lock or pass-through hatch. ~~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~~, ~~consideration~~	rooms for entering and leaving production areas should be used. Airlocks should be designed as follows: i. Personnel airlocks: Areas of increasing cleanliness used for entry of personnel (e.g. from the grade D area to the grade C area to the grade B area). In general hand washing facilities should be provided only in the first stage of the changing room and not be present in changing rooms directly accessing the grade B area. ii. Material airlocks: used for materials and equipment transfer. • Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process should be transferred into the grade A or grade B areas via an airlock or pass-through hatches. Equipment and materials (intended for use in the grade A area) should be protected when transiting through the grade B area. Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance. • Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with an active filtered air	

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~~should be given to listing these items on an authorized list.~~ Equipment and materials (intended for use in the grade A zone) should be protected when transiting through the grade B cleanroom. Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk ~~evaluation~~ assessment and mitigation measures ~~strategies~~ should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection ~~sanitisation~~ and monitoring ~~regime~~ programme approved by quality assurance. ● ~~Pass through hatches without active filtered air supply should be avoided. If necessary, provisions and procedures should be in place to avoid any risk of contamination (e.g. by the incoming material or by entering air)~~. Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with an active filtered air supply ● The movement of material from lower grade or unclassified area ~~clean not classified (CNC)~~ to ~~grade C~~ higher grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS ~~based on QRM principles, with cleaning~~	supply. • The movement of material or equipment from lower grade or unclassified area to higher-grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS.	

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~~and disinfection commensurate with the risk.~~		
~~5.10~~4.13 Both sets of doors for pass-throughs and airlocks (for material and personnel) ~~airlock doors~~ should not be opened simultaneously. ~~The opening of more than one door at a time should be prevented.~~ For airlocks leading to grade A zone and grade B areas, an interlocking system should ~~usually~~ be used. For airlocks leading to grade C and D cleanrooms, ~~at least~~ a visual and/or audible warning system should be operated as a minimum. Where required to maintain zone segregation, a time delay between the closing and opening of interlocked doors should be established.	4.13 For pass-through hatches and airlocks (for material and personnel), the entry and exit doors should not be opened simultaneously. For airlocks leading to the grade A and grade B areas, an interlocking system should be used. For airlocks leading to grade C and D areas, a visual and/or audible warning system should be operated as a minimum. Where required to maintain area segregation, a time delay between the closing and opening of interlocked doors should be established.	52. Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.
~~5.11~~4.14 ~~A HEPA or ULPA filtered air supply should~~ Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an air flow relative to ~~surrounding areas~~ background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure ~~differential of 10 – 15 Pascals~~ differentials of a minimum of 10 pascals (guidance values). Particular attention should be paid to the protection of the critical zone ~~of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed.~~ The recommendations regarding air supplies and pressure differentials may need to be modified where it ~~becomes~~ necessary to contain certain ~~some~~ materials, (e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials ~~or products~~.) The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating	4.14 Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure difference of a minimum of 10 Pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air-conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air	53. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10 – 15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various 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 and treatment

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surrounding areas. Decontamination of facilities（ e.g. the cleanrooms and HVAC）and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be from an area of the same grade.	should be from an area of the same or higher grade.	of air leaving a clean area may be necessary for some operations.
~~5.12~~4.15 ~~It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle generating person, operation or machine to a zone of higher product risk. 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, the need to demonstrate the air flow patterns should be based on a risk assessment~~ Airflow patterns within cleanrooms and zones should be visualised to demonstrate 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. 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 ~~under dynamic conditions~~ both at rest and in operation（ e.g. simulating operator interventions ）. Video recordings of the airflow patterns should be retained ~~are recommended~~. The outcome of the air visualisation studies should be considered when establishing the facility's environmental monitoring program.	4.15 Airflow patterns within cleanrooms and zones should be visualised to demonstrate 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 contamination to the higher grade areas. Where unidirectional airflow is required, visualisation studies should be performed to determine compliance, (see paragraphs 4.4 & 4.19). When filled, closed products are transferred to an adjacent cleanroom of a lower grade via a small egress point, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the grade B area. Where air movement is shown to be a contamination 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 documented and considered when establishing the facility's environmental monitoring programme.	54. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle generating person, operation or machine to a zone of higher product risk.

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~~5.13~~4.16 ~~A warning system should be provided to indicate failure in the air supply and reduction of pressure differentials below set limits. Indicators of pressure differences should be fitted between areas, based on QRM principles. These pressure differences should be recorded regularly or otherwise documented.~~ Indicators of pressure differences should be fitted between cleanrooms and/or isolators. Set-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 should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of pressure differentials (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other pressure differentials should be monitored and recorded at regular intervals.	4.16 Indicators of air pressure differences should be fitted between cleanrooms and/or between isolators and their background. Set points and the criticality of air pressure differences should be considered within the CCS. Air pressure differences identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differences (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other air pressure differences should be monitored and recorded at regular intervals.	55. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.
~~5.14~~4.17 ~~Consideration should be given to designing facilities that permit observation of activities from outside the clean 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.~~ Facilities should be designed to permit observation of production activities from outside the Grade A zone and Grade B area (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This	4.17 Facilities should be designed to permit observation of production activities from outside the grade A and B areas (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement should be considered when designing new facilities or during refurbishment of existing facilities.	N/A

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requirement should be considered when designing new facilities or during refurbishment of existing facilities.		
Barrier Technologies	**Barrier Technologies**	**Isolator technology**
~~5.15~~4.18 Isolator or ~~Restricted Access Barrier System~~ RABS technologies, and the associated processes, should be designed ~~so as~~ to provide ~~maximum~~ protection of the grade A environment. The ~~transfer~~ entry of materials during processing (and after decontamination) ~~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 and preferably supported by rapid transfer technologies or transfer isolators. ~~Any activities that potentially compromise the sterility assurance of the critical zone should be assessed and controls applied if they cannot be eliminated.~~	4.18 Isolators or RABS, which are different technologies, and the associated processes, should be designed to provide protection through separation of the grade A environment from the environment of the surrounding room. The hazards introduced from entry or removal of items during processing should be minimized and supported by high capability transfer technologies or validated systems that robustly prevent contamination and are appropriate for the respective technology.	22. The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices.
~~5.16~~4.19 The design of the RABS or isolator shall take into account all critical factors associated with these technologies including the quality of the air inside and the ~~surrounding area~~ background environment, the materials and component transfer, the decontamination, ~~disinfection~~ and/or sterilization processes, ~~and~~ the risk factors associated with the manufacturing operations and materials, and the operations conducted within the critical zone.	4.19 The design of the technology and processes used should ensure appropriate conditions are maintained in the critical zone to protect the exposed product during operations. i. Isolators: a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing. b. The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where	21. The utilisation of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating

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	simple operations are conducted. However, any turbulent airflow should not increase risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing c. Negative pressure isolators should only be used when containment of the product is considered essential (e.g. radiopharmaceutical products) and specialized risk control measures should be applied to ensure the critical zone is not compromised. ii. RABS: The design of RABS should ensure grade A conditions with unidirectional airflow and first air protection in the critical zone. A positive airflow from the critical zone to the supporting background environment should be maintained.	sterilisation mechanisms.
~~5.17~~4.20 The critical zone of the RABS or open isolator used for aseptic processes should meet grade A requirement with unidirectional air flow. 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. ~~Under certain circumstances turbulent airflow may be justified in a closed isolator when proven to have no negative impact on the product.~~ The design of the RABS and open isolators should ensure a positive airflow	4.20 The background environment for isolators or RABS should ensure the risk of transfer of contamination is minimized. i. Isolators: a. The background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should	

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from the critical zones to the ~~surrounding areas~~ supporting 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.	be based on risk assessment and justified in the CCS. b. Key considerations when performing the risk assessment for the CCS of an isolator should include (but are not limited to); the bio-decontamination programme, the extent of automation, the impact of glove manipulations that may potentially compromise 'first air' protection of critical process points, the impact of potential loss of barrier/glove integrity, transfer mechanisms used and activities such as set-up or maintenance that may require the doors to be opened prior to the final bio-decontamination of the isolator. Where additional process risks are identified, a higher grade of background should be considered unless appropriately justified in the CCS. c. Airflow pattern studies should be performed at the interfaces of open isolators to demonstrate the absence of air ingress. ii. RABS: The background environment for RABS used for aseptic processing should correspond to a minimum of grade B and airflow pattern studies should be performed to demonstrate the absence of air ingress during interventions, including door openings if applicable.	
~~5.18~~4.21 For RABS used for aseptic process, the background environment should meet at least grade B. The background environment for open Isolators should	N/A	

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meet Grade C or D, based on a risk assessment. Airflow studies should be performed to demonstrate the absence of air ingress during interventions, such as door openings. ~~for open RABS, or where doors may be very rarely opened during processing, and studies should be performed to demonstrate the absence of air ingress.~~		
~~5.19For open, positive pressure isolators or closed isolators with decontamination by a sporicidal agent, the surrounding area should correspond to a minimum of grade D. The disinfection regime should be included as a key consideration when performing the risk assessment to design the contamination control strategy for an isolator.~~	N/A	23. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing it should be at least grade D.
~~5.20 For isolators, the required background environment can vary depending on the design of the isolator, its application and the methods used to achieve bio-decontamination. The decision as to the supporting background environment should be documented in a risk assessment where additional risks are identified, such as for negative pressure isolators. Where items are introduced to the isolator after disinfection then a higher grade of background should be considered.~~	N/A	N/A
4.22 The background environment of a closed isolator should correspond to a minimum of Grade D. The disinfection/decontamination programme should be included as a key consideration when performing the risk assessment for the CCS of an isolator. Where additional process risks are identified, a higher grade of background should be considered. The decision as to the supporting background environment should be documented in the CCS.	N/A	23. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing it should be at least grade D.
~~5.21~~4.23 ~~Glove systems, as well as other parts of an~~	4.21 The materials used for glove systems (for both	25. Monitoring should be carried out

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~~isolator, are constructed of various materials that can be prone to puncture and leakage.~~ The materials used for glove systems (for both RABS and isolators), as well as other parts of an isolator shall be demonstrated to have good mechanical and chemical resistance.—Integrity testing of the barrier systems ~~and~~ leak testing of the glove system and the isolator ~~the isolator and the glove system~~ should be performed using ~~visual, mechanical and physical methods.~~ a methodology demonstrated to be suitable for the task and criticality. ~~They~~ 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 unit~~ 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. RABS gloves used in Grade A zone should be sterilized before installation and sterilized (or effectively decontaminated by a validated method which achieves the same objective) prior to each manufacturing campaign. The frequency of glove replacement should be defined within the CCS.	isolators and RABS), should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS. i. Isolators: a. For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length. Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system. For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session. b. Integrity / leak testing of isolator systems should be performed at defined intervals. ii. RABS: For RABS, gloves used in the grade A area should be sterilised before installation and sterilised or effectively bio-decontaminated by a validated method prior to	routinely and should include frequent leak testing of the isolator and glove/sleeve system.

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	each manufacturing campaign. If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed. Gloves should be visually examined with each use, and integrity testing should be performed at periodic intervals.	
~~5.22 Decontamination processes of an isolator or RABS should be validated and controlled in accordance with defined parameters. Evidence should also be available to demonstrate that the agent does not affect any process performed in the isolator or RABS, such as having an adverse impact on product or sterility testing.~~	N/A	24. Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.
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 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	4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator. i. For isolators The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. Methods	24. Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.

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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.	used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms. ii. For RABS The sporicidal disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly include all areas of the interior surfaces and ensure a suitable environment for aseptic processing.	
Cleanroom and clean air ~~device~~ equipment qualification	**Cleanroom and clean air equipment qualification**	**Clean room and clean air device classification**
~~5.23~~4.25 Cleanrooms and clean air equipment such as unidirectional airflow units (UDAFs), RABS and isolators, used ~~devices (clean areas)~~ for the manufacture of sterile products should be qualified and classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. ~~Note: Classification is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean area device by measuring the airborne particle concentration. The classification is part of the qualification of a clean area.~~	4.23 Cleanrooms and clean air equipment such as unidirectional airflow units (UDAFs), RABS and isolators, used for the manufacture of sterile products, should be qualified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risk of contamination of the product or materials being handled. Appropriate cleanliness levels in the “at rest” and “operational” states should be maintained.	3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.
~~5.24~~4.26 Clean rooms and clean air ~~devices~~ equipment should be qualified using methodology in accordance with	4.24 Cleanrooms and clean air equipment should be qualified using methodology in accordance with the	4. Clean rooms and clean air devices should be classified in accordance with EN

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the requirement of Annex 15~~ of EU GMP~~. Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring ~~Reference for the classification of the clean rooms and clean air devices can be found in the ISO 14644 series of standards.~~	requirements of Annex 15. Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring.	ISO 14644-1. Classification should be clearly differentiated from operational process environmental monitoring.
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 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. iii. Air pressure difference measurement. iv. Airflow direction and visualisation. v. Microbial airborne and surface contamination. vi. Temperature measurement. vii. Relative humidity measurement. viii. Recovery testing. ix. Containment leak testing.	4.25 Cleanroom and clean air equipment 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 Annex 15, the qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation): i. Installed filter system leakage and integrity testing. ii. Airflow tests - volume and velocity. iii. Air pressure difference test. iv. Airflow direction test and visualisation. v. Microbial airborne and surface contamination. vi. Temperature measurement test. vii. Relative humidity test. viii. Recovery test. ix. Containment leak test. Reference for the qualification of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards.	N/A
4.28 Cleanroom classification is part of a cleanroom qualification and is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the non-viable airborne particulate concentration. Reference for the classification	4.26 Cleanroom classification is part of the cleanroom qualification and is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the total particle concentration. Classification activities should be scheduled and performed	N/A

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<tr><td>of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards.</td><td>in order to avoid any impact on process or product quality. For example, initial classification should be performed during simulated operations and reclassification performed during simulated operations or during aseptic process simulation (APS).</td><td></td></tr>
<tr><td>~~5.25~~4.29 For cleanroom classification, the airborne particles equal to or greater than 0.5 µm and 5µm should be 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. 1 µm in accordance with ISO 14644 may be considered. This measurement should be performed both at rest and in operation. ~~This measurement should be performed both at rest and in operation~~. The maximum permitted airborne particle concentration for each grade is given in table 1.
Table 1:**Maximum permitted airborne ~~particle~~ particulate concentration during classification**
<table><tr><th colspan="6">~~Maximum permitted number of particles equal to or greater than 0.5 µm~~</th></tr><tr><th rowspan="2">Grade</th><th colspan="2">Maximum limits for particulates ≥0.5 µm/m³</th><th colspan="2">Maximum limits for particulates ≥5 µm/m³</th><th rowspan="2">~~ISO classification in operation/at rest~~</th></tr><tr><th>At rest ~~equal to or greater than 0.5 µm per m³~~</th><th>In operation ~~equal to or greater than 0.5 µm per m³~~</th><th>at rest</th><th>in operation</th></tr><tr><td>A</td><td>3 520</td><td>3 520</td><td>Not applicable</td><td>Not applicable</td><td>~~5/5~~</td></tr><tr><td>B</td><td>3 520</td><td>352 000</td><td>Not applicable</td><td>29000</td><td>~~5/7~~</td></tr><tr><td>C</td><td>352 000</td><td>3 520 000</td><td>2 900</td><td>29000</td><td>~~7/8~~</td></tr><tr><td>D</td><td>3 520 000</td><td>Not defined[a]</td><td>29 000</td><td>Not defined[a]</td><td>~~8~~</td></tr></table>[a]For grade D, ~~no~~ “in operation” limits are not defined; the company should establish in operation limits based on a risk assessment and on historical data, where applicable.</td><td>4.27 For cleanroom classification, the total of particles equal to or greater than 0.5 and 5 µm should be measured. This measurement should be performed both at rest and in simulated operations in accordance with the limits specified in Table 1.
Table 1: Maximum permitted total particle concentration for classification
<table><tr><th rowspan="2">Grade</th><th colspan="2">Maximum limits for total particle ≥ 0.5 µm/m³</th><th colspan="2">Maximum limits for total particle ≥ 5 µm/m³</th></tr><tr><th>at rest</th><th>in operation</th><th>at rest</th><th>in operation</th></tr><tr><td>A</td><td>3 520</td><td>3 520</td><td>Not specified [a]</td><td>Not specified [a]</td></tr><tr><td>B</td><td>3 520</td><td>352 000</td><td>Not specified [a]</td><td>2 930</td></tr><tr><td>C</td><td>352 000</td><td>3 520 000</td><td>2 930</td><td>29 300</td></tr><tr><td>D</td><td>3 520 000</td><td>Not predetermined [b]</td><td>29 300</td><td>Not predetermined [b]</td></tr></table>(a) Classification including 5µm particles may be considered where indicated by the CCS or historical trends.
(b) For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.</td><td>4. The maximum permitted airborne particle concentration for each grade is given in the following table.
<table><tr><th rowspan="2">Grade</th><th colspan="4">Maximum permitted number of particles per m³ equal to or greater than the tabulated size</th></tr><tr><th colspan="2">At rest</th><th colspan="2">In operation</th></tr><tr><th>0.5 µm</th><th>5.0µm</th><th>0.5 µm</th><th>5.0µm</th></tr><tr><td>A</td><td>3 520</td><td>20</td><td>3 520</td><td>20</td></tr><tr><td>B</td><td>3 520</td><td>29</td><td>352 000</td><td>2 900</td></tr><tr><td>C</td><td>352 000</td><td>2 900</td><td>3 520 000</td><td>29 000</td></tr><tr><td>D</td><td>3 520 000</td><td>29 000</td><td>Not defined</td><td>Not defined</td></tr></table></td></tr>
<tr><td>~~5.26~~4.30 For ~~initial~~ classification of the cleanroom, the</td><td>4.28 For classification of the cleanroom, the minimum</td><td>5. For classification purposes in Grade A</td></tr>
</table>

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minimum number of sampling locations and their positioning can be found in ISO 14644 Part 1. ~~However, a higher number of samples and sample volume is typically required~~ In addition, for the aseptic processing room and the ~~immediately adjacent~~ background environment (grade A zone and Grade B area, respectively ~~A/B~~), sample location should also ~~to include~~ consideration of all critical processing zone ~~locations~~ such as point of fill stopper bowls. ~~With the exception of the aseptic processing room, the sampling locations should be distributed evenly throughout the area of the clean room. For later stages of qualification and classification, such as performance qualification,~~ Critical processing locations should be based on a documented risk assessment and knowledge of the process and operations to be performed in the area.	number of sampling locations and their positioning can be found in ISO 14644 Part 1. For the aseptic processing area and the background environment (the grade A and grade B areas, respectively), additional sample locations should be considered and all critical processing areas such as the point of fill and container closure feeder bowls should be evaluated. Critical processing locations should be determined by documented risk assessment and knowledge of the process and operations to be performed in the area.	zones, a minimum sample volume of 1m^3 should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥5.0 µm. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes. . For Grade C (at rest & in operation) the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.
4.31 Clean room classification should be carried out in the “at rest” and “in operation” states. ~~a) The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms.~~ ~~b)~~ i. The definition of “at rest” state is the condition whereby the installation of all the utilities is ~~the room~~ complete ~~with all~~ including any functioning HVAC systems, ~~utilities functioning and~~ with the main manufacturing equipment installed as specified and standing by for operation, ~~but~~ without personnel in room ~~the facility and the manufacturing equipment is static~~. ~~c)~~ ii. The definition of “in operation” state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode	4.29 Cleanroom classification should be carried out in the “at rest” and “in operation” states. i. The definition of “at rest” state is the condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as specified but not operating and without personnel present in the room. ii. The definition of “in operation” state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode with the maximum number of personnel present performing or simulating routine	3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled. In order to meet “in operation” conditions these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. The “at-rest” state is the condition where the installation

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with the maximum number of personnel present performing or simulating routine operational work. In operation classification may be performed during simulated operations or during aseptic process simulations (where worst case simulation is required) ~~is functioning in the defined operating mode with the specified number of personnel working.~~ ~~d) "In operation" classification, qualification and requalification may be performed during normal operations, simulated operations or during aseptic process simulations (where worst case simulation is required).~~ ~~e)~~ iii. The particle limits given in Table 1 above for the "at rest" state should be achieved after a "clean up" period on completion of operations. The "clean up" period should be determined during the ~~initial~~ classification of the rooms（guidance value of 15 to 20minutes）. ~~f) In order to meet "in operation" conditions these areas should be designed to reach certain specified air cleanliness levels in the "at rest" occupancy state.~~	operational work. iii. The total particle limits given in Table 1 above for the "at rest" state should be achieved after a "clean up" period on completion of operations and line clearance/cleaning activities. The "clean up" period (guidance value of less than 20 minutes) should be determined during the qualification of the rooms, documented and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation.	is installed and operating, complete with production equipment but with no operating personnel present. The "in operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working. The "in operation" and "at rest" states should be defined for each clean room or suite of clean rooms. For the manufacture of sterile medicinal products 4 grades can be distinguished.
		7. "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.
		14. The particle limits given in the table for the "at rest" state should be achieved after a short "clean up" period of 15-20 minutes (guidance value) in an unmanned state after completion of operations.
4.32 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement	4.30 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement	N/A

<table>
<tr><th>2nd VS 1st</th><th>Final-20220825</th><th>Current Annex 1-2008</th></tr>
<tr><td>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 should correlate with the air speed measurement.</td><td>provides protection of the product and open components at the working position (e.g. where high-risk operations occur and where 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 should correlate with the air speed measurement.</td><td></td></tr>
<tr><td>~~5.27~~4.33 The microbial concentration ~~load~~ of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment, including the results of the classification, air visualization studies and knowledge of the process and operations to be performed in the area. The ~~recommended~~ maximum limits for microbial contamination during qualification for each grade are given in table 2. Qualification should include both at rest and in operation states.
Table 2: ~~Recommended~~ limits for microbial contamination ~~in operation~~ during qualification
<table>
<tr><th>Grade</th><th>air sample cfu/m3</th><th>settle plates (diameter 90 mm) cfu/4 hours (a)</th><th>contact plates (diameter 55 mm) cfu/plate</th></tr>
<tr><td>A (b)</td><td colspan="3">~~1~~ No growth (b)</td></tr>
<tr><td>B</td><td>10</td><td>5</td><td>5</td></tr>
<tr><td>C</td><td>100</td><td>50</td><td>25</td></tr>
<tr><td>D</td><td>200</td><td>100</td><td>50</td></tr>
</table>
(a) ~~Individual settle plates may be exposed for less than 4 hours. Where settle plates are exposed for less than 4 hours the limits in the table should still be used, no recalculation is necessary.~~ Settle plates should be exposed for the duration of ~~critical~~ operations and changed as required after 4 hours. Exposure time should</td><td>4.31 The microbial contamination level of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment and the results obtained from room classification, air visualization studies and knowledge of the process and operations to be performed in the area. The maximum limits for microbial contamination during qualification for each grade are given in Table 2. Qualification should include both “at rest” and “in operation” states.
Table 2: Maximum permitted microbial contamination level during qualification
<table>
<tr><th>Grade</th><th>Air sample CFU/m3</th><th>Settle plates (diameter 90 mm) CFU/4 hours (a)</th><th>Contact plates (diameter 55 mm) CFU/plate</th></tr>
<tr><td>A</td><td colspan="3">No growth</td></tr>
<tr><td>B</td><td>10</td><td>5</td><td>5</td></tr>
<tr><td>C</td><td>100</td><td>50</td><td>25</td></tr>
<tr><td>D</td><td>200</td><td>100</td><td>50</td></tr>
</table>
(a) Settle plates should be exposed for the duration of operations and changed as required after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

Note 1: All methods indicated for a specific grade in the table should be used for qualifying the area of that specific</td><td>19. Recommended limits for microbiological monitoring of clean areas during operation:
<table>
<tr><th></th><th colspan="4">Recommended limits for microbial contamination (a)</th></tr>
<tr><th>Grade</th><th>air sample cfu/m3</th><th>settle plates (diameter 90 mm) cfu/4 hours (b)</th><th>contact plates (diameter 55 mm) cfu/plate</th><th>glove print 5 fingers cfu/glove</th></tr>
<tr><td>A</td><td>< 1</td><td>< 1</td><td>< 1</td><td>< 1</td></tr>
<tr><td>B</td><td>10</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>C</td><td>100</td><td>50</td><td>25</td><td>-</td></tr>
<tr><td>D</td><td>200</td><td>100</td><td>50</td><td>-</td></tr>
</table>
Notes
(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.</td></tr>
</table>

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be based on recovery studies and should not allow desiccation of the media used. (b)It should be noted that for grade A the expected result should be ~~0 cfu recovered~~ no growth; any recovery of 1 cfu or greater should result in an investigation. Note 1: All methods indicated for a specific Grade in the table should be used for qualifying the area of that specific Grade. If one of the methods is not used, or alternative methods are used, the approach taken should be appropriately justified. Note 2: Limits are applied using cfu throughout the document. If different or new 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. Note 3: For qualification of personnel gowning, the limits given for contact plates and glove prints in Table 7 should apply ~~be applied.~~ Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.	grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified. Note 2: Limits are applied using CFU throughout the document. If different or new 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. Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply. Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.	
~~5.28 Clean room qualification (including classification) should be clearly differentiated from operational process environmental monitoring.~~	N/A	N/A
~~5.29 Clean rooms should be requalified periodically and after changes to equipment, facility or processes based on the principles of QRM. For grade A and B zones, the maximum time interval for requalification is 6 months. For~~	N/A	N/A

<table>
<tr><th>2nd VS 1st</th><th>Final-20220825</th><th>Current Annex 1-2008</th></tr>
<tr><td>~~grades C and D, the maximum time interval for requalification is 12 months.~~</td><td></td><td></td></tr>
<tr><td>4.34 The requalification of Clean rooms and clean air equipment should be carried out ~~requalified~~ periodically following defined procedures. The requirement for requalification of cleanroom areas is as follows: ~~and after changes to equipment, facility or processes based on the principles of QRM. For grade A and B zones, the maximum time interval for requalification is 6 months. For grades C and D, the maximum time interval for requalification is 12 months.~~
Table 3: Minimum test requirements for the requalification of cleanrooms
<table><tr><th>Grade</th><th>Determination of the concentration of airborne viable and non-viable particles</th><th>Integrity Test of Terminal Filters</th><th>Airflow volume measurement</th><th>Verification of air pressure difference between rooms</th><th>Air Velocity test</th></tr><tr><td>A</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td></tr><tr><td>B</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>*</td></tr><tr><td>C</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>*</td></tr><tr><td>D</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>*</td></tr></table>* performed according to a risk assessment documented as part of the CCS. However, required for filling zones (e.g. when filling terminally sterilised products) and background to Grade A RABS.

For Grade A & B areas, the maximum time interval for requalification is 6 months.
For Grade C & D areas, the maximum time interval for requalification is 12 months.

Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out-of-</td><td>4.32 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requalification should include at a minimum the following:
- Cleanroom classification (total particle concentration).
- Integrity test of final filters.
- Airflow volume measurement.
- Verification of air pressure difference between rooms.
- Air velocity test (Note: For grade B, C and D the air velocity test should be performed according to a risk assessment documented as part of the CCS. However, it is required for filling zones supplied with unidirectional airflow (e.g. when filling terminally sterilised products or background to grade A and RABS). For grades with non-unidirectional airflow, a measurement of recovery testing should replace velocity testing).

The maximum time interval for requalification of grade A & B areas, is 6 months.
The maximum time interval for requalification of grade C & D areas, is 12 months.

Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out of compliance equipment or facility condition or after changes to equipment, facility or processes as appropriate. The significance of a change should be determined through the</td><td>N/A</td></tr>
</table>

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compliance equipment or facility condition or after changes to equipment, facility or processes. The significance of a change should be determined through the change management process. Examples of changes to be considered include but are not limited to the following: i. Change in the operational use of the cleanroom, or of the operational setting parameters of the HVAC system. ii. Interruption of air movement which affects the operation of the installation. iii. Special maintenance which affects the operation of the installation (e.g. change of final filters).	change management process. Examples of changes to be considered include but are not limited to the following: i. Interruption of air movement which affects the operation of the installation. ii. Change in the design of the cleanroom or of the operational setting parameters of the HVAC system. iii. Special maintenance which affects the operation of the installation (e.g. change of final filters).	
~~5.30~~4.35 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 standards (e.g. Grade A or B)~~depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard~~.	转至 9.6	16. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.
Disinfection	**Disinfection**	**Sanitation**
~~5.31~~4.36 The disinfection of ~~clean areas~~ cleanroom is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should ~~must~~ be performed first. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action and their combined usage is	4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. Cleaning programmes should effectively remove disinfectant residues. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their	61. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

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effective against all bacteria and fungi. ~~and~~ Disinfectants should include the periodic use of a sporicidal agent. ~~Disinfectants should be shown to be effective for the duration of their in-use shelf life taking into consideration appropriate contact time and the manner in and surfaces on which they are utilized.~~ Monitoring should be undertaken regularly in order to ~~show~~ assess the effectiveness of the disinfection program and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use). ~~the development of resistant and/or spore forming strains~~. *Cleaning programs should effectively remove ~~be effective in the removal of~~ disinfectant residues.*	combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection programme and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use).	
4.37 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and should support the in-use expiry periods of prepared solutions.	4.34 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions.	N/A
~~5.32~~4.38 Disinfectants and detergents used in Grade A zone and Grade B areas should be sterile prior to use (disinfectants used in Grade C and D may also be required to be sterile) Where the disinfectants and detergents are made up by the sterile product manufacturer, they should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods. ~~Disinfectants and detergents used in grade A and B areas should be sterile prior to use.~~ If the disinfectants and detergents are supplied “ready-made” then results from certificates of analysis or conformance can be accepted subject to successful	4.35 Disinfectants and detergents used in grade A and grade B areas should be sterile prior to use. Disinfectants used in grade C and D may also be required to be sterile where determined in the CCS. Where the disinfectants and detergents are diluted / prepared by the sterile product manufacturer, this should be done in a manner to prevent contamination and they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers (and sterilized where applicable) and should only be stored for the defined period. If the disinfectants and detergents are supplied “ready-made” then results from certificates of analysis or conformance can be accepted subject to successful completion of the	62. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

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completion of the appropriate vendor qualification.	appropriate vendor qualification.	
~~5.33 Disinfectants should be shown to be effective when used on the specific facilities, equipment and processes that they are used in.~~	N/A	N/A
~~5.34~~4.39 Fumigation or vapour disinfection (e.g. Vapour-phased Hydrogen Peroxide) of cleanroom and associated surfaces ~~areas such as Vapour Hydrogen Peroxide (VHP)~~ may be useful for reducing microbiological contamination in inaccessible places.	4.36 Where fumigation or vapour disinfection (e.g. Vapour-phase Hydrogen Peroxide) of cleanrooms and associated surfaces are used, the effectiveness of any fumigation agent and dispersion system should be understood and validated.	63. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

5. Equipment

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5.1 A written, detailed description of the equipment design should be available ~~produced~~ (including process and instrumentation diagrams as appropriate) ~~and be kept up to date~~ ~~It~~ This should ~~describe the product and other critical gas and fluid pathways and controls in place.~~ form part of the initial qualification package and be kept up to date as part of the ongoing review of the CCS.	5.1 A written, detailed description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification package and be kept up to date.	N/A
5.2 Equipment monitoring requirements should be ~~determined~~ defined in "user requirements specifications" and during early stages of development, and confirmed during qualification. Process and equipment alarm events should be reviewed and approved and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).	5.2 Equipment monitoring requirements should be defined in "user requirements specifications" during early stages of development, and confirmed during qualification. Process and equipment alarm events should be acknowledged and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).	N/A
5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed ~~carried out~~ outside the clean area~~,~~. ~~I~~If maintenance has to be performed in the cleanroom ~~clean area~~ and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered. Cleaning, additional disinfection and additional environmental monitoring should be considered. If sterilization of equipment is required, it should be carried out, wherever possible, after complete reassembly.	5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be considered. If sterilisation of equipment is required, it should be carried out, wherever possible, after complete reassembly.	57. As far as practicable equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out, wherever possible, after complete reassembly.
5.4 The cleaning process should be validated to ~~so that~~	5.4 The cleaning process should be validated to be able to:	N/A

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~~it can be demonstrated that it~~: a) ~~Can r~~Remove any residues or debris that would ~~otherwise create a barrier between the sterilizing agent and the equipment surfaces.~~detrimentally impact the effectiveness of the disinfecting agent used. b) ~~Prevents~~ Minimize chemical and particulate contamination of the product during the process and prior to disinfection.	i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used. ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.	
~~6.4 When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilized where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.~~	N/A	58. When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.
5.5 Direct and indirect contact parts should be sterilized. Direct contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that come into contact with sterilized critical items and components.	5.5 For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).	N/A
~~6.6 All critical surfaces that come into direct contact with sterile materials should be sterile.~~		N/A
5.6 All equipment such as sterilizers, air handling systems (including air filtration) and ~~filtration systems,~~ water ~~treatment, generation, storage and distribution~~	5.6 All equipment such as sterilisers, air handling systems (including air filtration) and water systems should be subject to qualification, monitoring and planned maintenance. Upon	60. All equipment such as sterilisers, air handling and filtration systems, air vent and gas filters, water treatment,

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systems should be subject to qualification, monitoring and planned maintenance; Upon completion of maintenance, their return to use should be approved.	completion of maintenance, their return to use should be approved.	generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.
5.7 Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.	5.7 Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.	N/A
5.8 A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (e.g. in a sterilizing tunnel).	5.8 A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).	56. A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).
5.9 Particle counters, including sampling tubing should be qualified ~~(including sampling tubing)~~. 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 qualification purposes. Isokinetic sample heads shall 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, should be qualified. The manufacturer's recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1m unless justified and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.	**Clean room and clean air device classification** 6. Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0μm in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems. 11. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the

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		particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example those involving live organisms or radiopharmaceuticals.

6. Utilities

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~~7.1~~6.1 The nature and ~~amount~~ extent of controls ~~associated with utilities~~ applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment documented as part of the CCS.	6.1 The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment and documented as part of the CCS.	N/A
~~7.2~~6.2 In general higher risk utilities are those that: i. Directly contact product e.g. ~~compressed~~ water for washing and rinsing, gases and steam for sterilization. ii. Contact materials that will ultimately ~~will~~ become part of the product. iii. ~~Control contamination of~~ Contact surfaces that come into contact with the product. iv. ~~Or~~ Otherwise directly impact the product.	6.2 In general, higher risk utilities are those that: i. Directly contact product e.g. water for washing and rinsing, gases and steam for sterilisation. ii. Contact materials that will ultimately become part of the product. iii. Contact surfaces that come into contact with the product. iv. Otherwise directly impact the product.	N/A
~~7.3~~6.3 Utilities should be designed, installed, operated ~~and~~ maintained and monitored in a manner to ensure that the utility functions as expected.	6.3 Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected.	N/A
~~7.4~~6.4 Results for critical parameters and critical quality attributes of ~~the~~ high risk ~~utility~~ utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.	6.4 Results for critical parameters and critical quality attributes of high risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.	N/A
~~7.5~~6.5 Records of utility installation should be maintained throughout the system's life-cycle. Such records should include current drawings ~~should be available that identify critical system~~ and schematic diagrams, construction material lists and specifications. Typically, important information includes attributes such as:	6.5 Records of utility system installation should be maintained throughout the system's life-cycle. Such records should include current drawings and schematic diagrams, construction material lists and system specifications. Typically, important information includes attributes such as: i. Pipeline flow direction, slopes, diameter and length.	N/A

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i. Pipeline flow~~, pipeline~~ direction, slopes, ~~pipeline~~ diameter and length~~, tanks, .~~ ii. Tank and vessel details. iii. Valves, filters, drains ~~and~~, sampling and user points.	ii. Tank and vessel details. iii. Valves, filters, drains, sampling and user points.	
~~7.6~~6.6 Pipes ~~and~~, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.	6.6 Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.	**Premises** 49. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.
Water systems	**Water systems**	**N/A**
~~7.7~~6.7 Water treatment ~~plants~~ plant and distribution systems should be designed, constructed and maintained to minimize the risk of particulates, microbial contamination ~~and~~ /proliferation ~~so as~~ and pyrogens (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs), and prevent the formation of biofilms to ensure a reliable source of water of an appropriate quality. Where filters are included in 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.	6.7 Water treatment plant and distribution systems should be designed, constructed, installed, commissioned, qualified, monitored and maintained to prevent microbiological contamination and to ensure a reliable source of water of an appropriate quality. Measures should be taken to minimize the risk of presence of particulates, microbial contamination/proliferation and endotoxin/pyrogen (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs). Where filters are included in the system, special attention should be given to their monitoring and maintenance. Water produced should comply with the current monograph of the relevant Pharmacopeia.	**Equipment** 59. Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C. Processing 72. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records

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		should be maintained of the results of the monitoring and of any action taken.
~~7.8 Water for injections (WFI) should be produced from purified water, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70C. Where the WFI is produced by methods other than distillation further techniques post Reverse osmosis (RO) membrane should be considered such as nanofiltration, and ultra-filtration.~~	N/A	
~~7.9~~6.8 Water systems should be ~~validated~~ qualified to maintain the appropriate levels of physical, chemical and microbial control, taking seasonal variation into account.	6.8 Water systems should be qualified and validated to maintain the appropriate levels of physical, chemical and microbial control, taking the effect of seasonal variation into account.	N/A
~~7.10~~6.9 Water flow should remain turbulent through the pipes to ~~prevent~~ minimize the risk of microbial adhesion, and subsequent biofilm formation.	6.9 Water flow should remain turbulent through the pipes in water distribution systems to minimize the risk of microbial adhesion, and subsequent biofilm formation. The flow rate should be established during qualification and be routinely monitored.	N/A
~~7.11 The water system should be configured to prevent the proliferation of microorganisms, e.g. sloping of piping to provide complete drainage and the avoidance of dead legs. Where filters are included in the system, special attention should be taken with regards to the monitoring and maintenance of these filters.~~	N/A	N/A
6.10 Water for injections (WFI) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner which minimizes the risk of microbial growth (for example by constant circulation at a temperature above 70°C). Where the WFI is produced by methods other than distillation, further techniques such as nanofiltration and	6.10 Water for injections (WFI) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner which minimizes the risk of microbial growth (e.g. by constant circulation at a temperature above 70°C). WFI should be produced by distillation or by a purification process that is equivalent to distillation. This may include	**Equipment** 59. Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity.

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ultra-filtration as well as electrodeionization (EDI) should be considered in conjunction with reverse osmosis (RO) membranes.	reverse osmosis coupled with other appropriate techniques such as electrodeionization (EDI), ultrafiltration or nanofiltration.	Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.
~~7.12~~6.11 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should be sterilized and the integrity of the filter tested before installation and after removal following use.	6.11 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should not be a source of contamination and the integrity of the filter tested before installation and after use. Controls should be in place to prevent condensation formation on the filter (e.g. by heating).	N/A
~~7.13~~6.12 To ~~prevent~~ minimize the risk of biofilm 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/flushing procedure. Water should be ~~analyzed~~ tested after disinfection/regeneration. The results should be approved before the ~~start of use of the~~ water system is returned to use.	6.12 To minimize the risk of biofilm formation, sterilisation, disinfection or regeneration of water systems should be carried out according to a predetermined schedule and as a remedial action following out-of-limit or specification results. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure. Water should be tested after disinfection/regeneration. Chemical testing results should be approved before the water system is returned to use and microbiological/endotoxin results verified to be within specification and approved before batches manufactured using water from the system are considered for certification/release.	N/A
~~7.14 A suitable sampling schedule should be in place to ensure that representative water samples are obtained for analysis on a regular basis.~~	N/A	N/A
~~7.15~~6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed ~~with alert limits~~. Alert levels should be based on the qualification or a review of ongoing monitoring data that will identify an	6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed to ensure that the water continues to meet compendial expectations. Alert levels should be based on the initial qualification data and	N/A

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adverse trend in ~~the~~system performance ~~of the systems.~~. Sampling programs should reflect the requirements of the CCS and include ~~all outlets and user~~: 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 ~~worst case sample~~ point~~, e.g.~~ at the end of the distribution loop ~~return, should be included~~ each ~~time~~ day that the water is used ~~for manufacturing and manufacturing processes. A breach~~.	thereafter periodically reassessed on data obtained during subsequent re-qualifications, routine monitoring, and investigations. Review of ongoing monitoring data should be carried out to identify any adverse trend in system performance. Sampling programmes should reflect the requirements of the CCS and should include all outlets and points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis. Sample plans should be based on the qualification data, should consider the potential worst case sampling locations and should ensure that at least one representative sample is included every day of the water that is used for manufacturing processes.	
6.14 Breaches of ~~an~~ alert ~~limit~~ levels should ~~trigger review~~ be documented and reviewed, and ~~follow up, which might~~ include investigation ~~and corrective action. Any~~ of system trends to determine whether the breach is a single (isolated) event or if results are indicative of loss of control or system deterioration. Each breach of ~~an~~ action ~~limit~~ limits should ~~lead~~ be investigated to ~~a~~ determine the root cause ~~investigation and risk assessment.~~ of the issue and any impact on the quality of products and manufacturing processes as a result of the potential use of the water.	6.14 Alert level excursions should be documented and reviewed, and include an investigation to determine whether the excursion is a single (isolated) event or if results are indicative of an adverse trend or system deterioration. Each action limit excursion should be investigated to determine the probable root causes and any potential impact on the quality of products and manufacturing processes as a result of the use of the water.	N/A
~~7.16~~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.	6.15 WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity, as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk.	N/A
Steam used ~~for sterilization~~ as a direct sterilizing agent	**Steam used as a direct sterilising agent**	**N/A**

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~~7.17 Purified water, with a low level of endotoxin, should be used as the minimum quality feed water for the pure steam generator.~~	N/A	N/A
6.16 Feed water to a pure steam (clean steam) generator should be appropriately purified. Pure steam generators should be designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels.	6.16 Feed water to a pure steam (clean steam) generator should be appropriately purified. Pure steam generators should be designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels.	N/A
~~7.18~~6.17 Steam used ~~for sterilization processes~~ as a direct sterilizing agent should be of suitable quality and should not contain additives at a level which could cause contamination of product or equipment. ~~The quality of~~ 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 ~~and for Steam-In-Place (SIP)~~), steam condensate should meet the current monograph for WFI of the relevant Pharmacopeia. A suitable sampling schedule should be in place to ensure that representative pure steam samples are obtained for analysis on a regular basis. Other aspects of the quality of pure steam used for sterilization should be assessed periodically against validated parameters. These parameters should include ~~consideration of~~ the following ~~examples~~: non-condensable gases, dryness value (dryness fraction~~),~~) and superheat ~~and steam condensate quality.~~ .	6.17 Steam used as a direct sterilising agent should be of suitable quality and should not contain additives at a level that could cause contamination of product or equipment. For a generator supplying pure steam used for the direct sterilisation 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 (microbial testing is not mandatory for steam condensate). A suitable sampling schedule should be in place to ensure that representative pure steam is obtained for analysis on a regular basis. Other aspects of the quality of pure steam used for sterilisation should be assessed periodically against validated parameters. These parameters should include the following (unless otherwise justified): non-condensable gases, dryness value (dryness fraction) and superheat.	96. Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.
~~Compressed~~ **Gases and vacuum systems**	**Gases and vacuum systems**	**N/A**
~~7.19~~ 6.18~~Compressed~~ Gases that come in direct contact with the product/primary container ~~primary~~ surfaces should be of appropriate chemical, particulate and ~~microbiological purity, free from~~ microbial quality. All relevant parameters, including oil ~~with~~ and water content, should be specified,	6.18 Gases that come in direct contact with the product/primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, should be specified, taking into account the use and type of the	N/A

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taking into account the ~~correct dew point specification and,~~ use and type of the gas, the design of the gas generation system and, where applicable, comply with the appropriate ~~pharmacopoeial~~ Pharmacopoeia 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. Where used for aseptic manufacturing, confirmation of the integrity of the final sterilization gas filter should be considered as part of the batch release process.~~	gas, the design of the gas generation system and, where applicable, comply with the current monograph of the relevant Pharmacopeia or the product quality requirement.	
6.19 Gases used in aseptic processes should be filtered through a sterilizing filter (with a nominal pore size of a maximum of 0.22 µm) at the point of use. Where ~~used~~ the filter is used on a batch basis (e.g. for ~~aseptic manufacturing, confirmation of the~~ filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity ~~of the final sterilization gas filter should be considered~~ tested and the results included as part of the batch ~~release~~ certification process. Any transfer pipework or tubing that is located after the final sterilizing filter should be sterilized. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.	6.19 Gases used in aseptic processes should be filtered through a sterilising grade filter (with a nominal pore size of a maximum of 0.22 µm) at the point of use. Where the filter is used on a batch 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 reviewed as part of the batch certification/release process. Any transfer pipework or tubing that is located after the final sterilising grade filter should be sterilised. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.	N/A
~~7.20~~6.20 ~~There should be prevention of~~ Where backflow from vacuum or pressure systems poses a potential risk to the product, there should be mechanism(s) to prevent backflow when ~~any~~ the vacuum or pressure system is shut off.	6.20 Where backflow from vacuum or pressure systems poses a potential risk to the product, there should be mechanism(s) to prevent backflow when the vacuum or pressure system is shut off.	N/A
~~Cooling~~ Heating and cooling and hydraulic systems	**Heating and cooling and hydraulic systems**	**N/A**
~~7.21~~6.21 Major items of equipment associated with hydraulic, heating and cooling systems, e.g. such as those associated with Blow-Fill-Seal equipment should, where	6.21 Major items of equipment associated with hydraulic, heating and cooling systems should, where possible, be located outside the filling room. There should be	N/A

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possible, be located outside the filling room. Where they are located inside the filling room there should be appropriate controls to contain any spillage and/or cross contamination associated with the ~~hydraulics of cooling~~ hydraulic system fluids. Where possible, the system should be at a lower pressure than the processed fluid.	appropriate controls to contain any spillage and/or cross contamination associated with the system fluids.	
~~7.22~~6.22 Any leaks from ~~the cooling system must be~~ these systems that would present a risk to the product should be detectable (i.e. an indication system for leakage). ~~In addition, there must be adequate cooling flow within the system.~~	6.22 Any leaks from these systems that would present a risk to the product should be detectable (e.g. an indication system for leakage).	N/A
~~7.23 The cooling circuit should be subject to leak testing both periodically and following any maintenance.~~	N/A	N/A
~~7.24~~6.23 ~~The cooling circuit should be subject to leak testing~~ For both ~~periodically and following any maintenance~~. vacuum and cooling systems there should be periodic cleaning/disinfection ~~of both the vacuum system and cooling systems.~~ as determined in the CCS.	N/A	N/A

7. Personnel

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~~4.1~~7.1 The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products ~~medicines~~ and any of the specific manufacturing technologies used in the site's manufacturing operations, to ensure compliance with GMP applicable to the manufacture and handing of sterile ~~medicinal~~ products.	7.1 The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products, and any of the specific manufacturing technologies used in the site's manufacturing operations, to ensure compliance with GMP applicable to the manufacture and handling of sterile products.	N/A
~~4.2~~7.2 Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms ~~critical areas~~ should be determined ~~based on QRM principles~~, documented ~~in the contamination control strategy,~~ and validated during activities such as initial qualification and aseptic process simulations, so as not to compromise sterility assurance. This is particularly important during aseptic processing. ~~Inspections and controls should be conducted outside the clean areas as far as possible.~~	7.2 Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms should be determined, documented and considered during activities such as initial qualification and APS, so as not to compromise sterility assurance.	36. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.
7.3 Non-essential processes such as product inspection and in process testing should be conducted outside the clean areas wherever possible.		N/A
~~4.3~~7.4 All personnel including those performing cleaning, maintenance monitoring and those that access cleanrooms ~~employed in such areas~~ should receive regular training, gowning qualification ~~(including sampling of the operators bioburden, using methods such as contact plates, at key locations e.g. hands arms and chest)~~ and assessment in disciplines relevant to the correct manufacture of sterile products.	7.3 All personnel including those performing cleaning, maintenance, monitoring and those that access cleanrooms should receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include the basic elements of microbiology and hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques and the protection of sterile	37. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g.

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This training should include the basic elements of microbiology, ~~reference to~~ hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques, and the protection of sterile products (for those operators entering the Grade B cleanrooms and/or intervening into the Grade A zone) and the potential safety implications to the patient ~~of a loss of product sterility and in the basic elements of microbiology.~~ if product is not sterile, the level of training should be based on the criticality of the function and area in which the personnel are working.	products (for those operators entering the grade B cleanrooms and/or intervening into grade A) and the potential safety implications to the patient if the product is not sterile. The level of training should be based on the criticality of the function and area in which the personnel are working.	building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.
~~4.4~~7.5 The personnel working in a grade A zone and Grade B areas should be trained for aseptic gowning and aseptic practices. Compliance with aseptic gowning procedures should be assessed and confirmed periodically reassessed at least annually and should involve both visual and microbial ~~microbiological~~ assessment (using monitoring ~~additional~~ locations such as hands, arms, ~~and~~ chest and forehead, refer to paragraph9.30 for the expected limits). 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, ~~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 grade A/B area, in which aseptic operations will be conducted, or are being conducted, whilst unsupervised. The microbial monitoring of personnel in the grade A/B area~~	7.4 The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment (using monitoring locations such as gloved fingers, forearms, chest and hood (facemask / forehead). See paragraph 9.30 for the expected limits). The unsupervised access to the grade A 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 APS.	N/A

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~~should be performed to assess their aseptic behaviour. This monitoring should take place immediately after completion of a critical intervention and upon each exit from the cleanroom. It should be noted that there should also be an ongoing continuous monitoring program for personnel including some consideration of periodic monitoring under the supervision of the quality unit.~~		
~~4.6~~7.6 Unqualified personnel (e.g. building and maintenance contractors and regulatory inspectors) should not enter Grade B cleanrooms or Grade A zones in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified personnel are brought into the Grade B and A areas. *Access by these persons should be assessed and recorded in accordance with the PQS.* An authorized person from the manufacturer should supervise the unqualified personnel during their activities and should assess the impact of these activities on the cleanliness of the area.	7.5 Unqualified personnel should not enter grade B cleanrooms or grade A in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified personnel are brought into the grade B and A areas. An authorized person from the manufacturer should supervise the unqualified personnel during their activities and should assess the impact of these activities on the cleanliness of the area. *Access by these persons should be assessed and recorded in accordance with the PQS.*	37. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.
~~4.5~~7.7 There should be systems in place for disqualification of personnel from entry into cleanrooms, based on aspects including ongoing assessment and/or the identification of an adverse trend from the personnel monitoring program and/or after participation in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering Grade B cleanrooms or performing intervention into Grade A zone, this requalification ~~This~~	7.6 There should be systems in place for the disqualification of personnel from working in or given unsupervised entry into cleanrooms that is based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring programme and/or after being implicated in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering grade B cleanrooms or performing intervention into grade A, this requalification should include consideration of participation in a successful	N/A

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should include consideration of participation in a successful Aseptic Process Simulation (APS).	APS.	
~~4.7~~7.8 High standards of personal hygiene and cleanliness are essential to prevent excessive shedding or increased risk of introduction of microbial contamination. Personnel involved in the manufacture of sterile products ~~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; health conditions and actions to be taken with regard to personnel who could be introducing an undue microbial ~~microbiological~~ hazard should be decided provided by a designated competent person and described in procedures.	7.7 High standards of personal hygiene and cleanliness are essential to prevent excessive shedding or increased risk of introduction of microbial contamination. Personnel involved in the manufacture of sterile products should be instructed to report any specific health conditions or ailments that may cause the shedding of abnormal numbers or types of contaminants and therefore preclude cleanroom access. Health conditions and actions to be taken with regard to personnel who could be introducing an undue microbial hazard should be provided by the designated competent person and described in procedures.	39. High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.
~~4.8~~7.9 Staff who have been engaged in the processing of human or animal tissue materials or of cultures of micro-organisms, other than those used in the current manufacturing process, or any activities that may have a negative impact to quality, (e.g. microbial contamination), should not enter ~~sterile product~~ clean areas unless ~~rigorous,~~ clearly defined and effective decontamination and entry procedures have been followed.	7.8 Personnel who have been engaged in the processing of human or animal tissue materials or of cultures of micro-organisms, other than those used in the current manufacturing process, or any activities that may have a negative impact to quality (e.g. microbial contamination), should not enter clean areas unless clearly defined and effective decontamination and entry procedures have been followed and documented.	38. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.
~~4.9~~7.10 Wristwatches, make-up and jewellery and other personal items such as mobile phones any other non-essential items should not be allowed in clean areas. Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the company solely for use in the cleanrooms, may be acceptable if suitably designed to permit cleaning and	7.9 Wristwatches, make-up, jewellery, other personal items such as mobile phones and any other non-essential items should not be allowed in clean areas. Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the manufacturer solely for use in the cleanrooms, may be acceptable if suitably designed to permit cleaning and disinfection commensurate with the	40. Wristwatches, make-up and jewellery should not be worn in clean areas.

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disinfection commensurate with the Grade in which they are used. The use and disinfection of such equipment should be included in the CCS.	grade in which they are used. The use and disinfection of such equipment should be included in the CCS.	
~~4.10~~7.11 Cleanroom gowning and hand washing should follow a written procedure designed to minimize contamination of cleanroom clothing and/or the transfer of contaminants to the clean areas. ~~Garments should be visually checked for cleanliness and integrity prior to entry to the clean room. For sterilized garments, particular attention should be taken to ensure that garments and eye coverings have been sterilized and that their packaging is integral before use. Reusable garments should be replaced based at a set frequency determined by qualification or if damage is identified.~~	7.10 Cleanroom gowning and hand washing should follow a written procedure designed to minimize ontamination of cleanroom clothing and/or the transfer of contaminants to the clean areas.	41. Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.
~~4.11~~7.12 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. When the type of clothing chosen needs to provide the operator protection from the product, it should not compromise the protection of the product from contamination. Garments should be visually checked for cleanliness and integrity immediately prior to gowning and prior to entry to the cleanroom. Gown integrity should also be checked upon exit. For sterilized or effectively decontaminated garments and eye coverings, particular attention should be taken to ensure they have been processed, are within their specified hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments	7.11 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. When the type of clothing chosen needs to provide the operator protection from the product, it should not compromise the protection of the product from contamination. Garments should be visually checked for cleanliness and integrity immediately prior to and after gowning. Gown integrity should also be checked upon exit. For sterilised garments and eye coverings, particular attention should be taken to ensure they have been subject to the sterilisation process, are within their specified hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments (including eye coverings) should be replaced if damage is identified, or at a set frequency that is determined during qualification	42. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

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(including eye coverings) should be replaced if damage is identified or at a set frequency that is determined during qualification studies. . Damage to garments may not be identified by visual inspection alone, so the qualification should consider any necessary garment testing requirements.	studies. The qualification of garments should consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.	
7.13 Clothing should be chosen to prevent shedding due to operators moving excessively (when cold) or sweating (when hot).	7.12 Clothing should be chosen to limit shedding due to operators' movement.	N/A
~~4.12~~7.14 The description of clothing required for each grade is given below:	7.13 A description of typical clothing required for each cleanliness grade is given below:	43. The description of clothing required for each grade is given below:
a) Grade A/B: Dedicated garments to be worn under a sterilized suit. Sterile 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 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 particles. Appropriate sterilized, non-powdered rubber ~~or~~ plastic gloves and sterilized footwear (such as overboots) should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should minimize shedding of 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~~ gown without contacting to the outer surfaces of the garment ~~reduced to a minimum~~.	i. Grade B (including access / interventions into grade A): appropriate garments that are dedicated for use under a sterilised suit should be worn before gowning (see paragraph 7.14). Appropriately sterilised, non-powdered, rubber or plastic gloves should be worn while donning the sterilised garments. Sterile 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 facemask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. Appropriate sterilised footwear (e.g. over-boots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown. The protective clothing should minimize shedding of fibres or particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be	Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected 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.

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	assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.	
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 shoes or overshoes should be worn. They should minimize the shedding of fibres or particulate matter.	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 shoes or overshoes should be worn. They should minimize the shedding of fibres and particles.	Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.
c) 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 ingress of contamination from outside the clean area.	iii. 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 ingress of contaminants from outside the clean area.	Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.
d) Gloves should be worn in Grade C and D areas when performing activities considered to be a contamination risk as defined by the CCS.	iv. Additional gowning including gloves and facemask may be required in grade C and D areas when performing activities considered to be a contamination risk as defined by the CCS.	N/A
~~Note: This is minimum guidance and higher standards of clothing may be required dependent on the processes performed in the specific area.~~	N/A	N/A
~~4.13~~7.15 Outdoor clothing (other than personal underwear) should not be brought into changing rooms leading directly to grade B and C rooms. ~~It is recommended that~~ Facility suits, covering the full length of the arms and the legs, and socks covering the feet, should ~~including dedicated socks~~ be worn before entry to change rooms for grade B and C.	7.14 Cleanroom gowning should be performed in change rooms of an appropriate cleanliness grade to ensure gown cleanliness is maintained. Outdoor clothing including socks (other than personal underwear) should not be brought into changing rooms leading directly to grade B and C areas. Single or two-piece facility trouser suits, covering the full length of the arms and the legs, and facility socks covering	44. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations.

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~~Where clothing is reused this should be considered as part of the qualification~~. Facility suits and socks should not present a risk of contamination to the gowning area or processes.	the feet, should be worn before entry to change rooms for grades B and C. Facility suits and socks should not present a risk of contamination to the gowning area or processes.	Masks and gloves should be changed at least for every working session.
~~4.14~~7.16 ~~For~~ 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 work entry ~~session~~. The maximum duration of each garment use should be defined as part of the garment qualification.	7.15 Every operator entering grade B or A areas should gown into clean, sterilised protective garments (including eye coverings and masks) of an appropriate size at each entry. The maximum period for which the sterilised gown may be worn before replacement during a shift should be defined as part of the garment qualification.	N/A
7.17 Garments and gloves should be changed ~~at least for every working session~~ immediately if they become damaged and present any risk of product contamination. Gloves should be regularly disinfected during operations.	7.16 Gloves should be regularly disinfected during operations. Garments and gloves should be changed immediately if they become damaged and present any risk of product contamination.	N/A
~~4.15~~7.18 Clean area clothing should be cleaned in a dedicated laundry facility using a qualified process ensuring that the clothing is not damaged and/or contaminated by fibres and particles during the laundry process. ~~handled and worn in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable~~. Inappropriate ~~treatment~~ handing and use of clothing will damage fibres and may increase the risk of shedding of particles. After washing and before ~~sterilization~~ packing, garments should be ~~checked for integrity~~ visually inspected for damage. The garment management processes should be evaluated and determined as part of the garment qualification program.	7.17 Reusable clean area clothing should be cleaned in a laundry facility adequately segregated from production operations, using a qualified process ensuring that the clothing is not damaged and/or contaminated by fibres or particles during the repeated laundry process. Laundry facilities used should not introduce risk of contamination or cross-contamination. Inappropriate handling and use of clothing may damage fibres and increase the risk of shedding of particles. After washing and before packing, garments should be visually inspected for damage and visual cleanliness. The garment management processes should be evaluated and determined as part of the garment qualification programme and should include a maximum number of laundry and sterilisation cycles.	45. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

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~~4.16~~7.19 Activities in clean areas that are not critical to the production processes, should be kept to a minimum, especially when aseptic operations are in progress. Movement of personnel should be slow, controlled and methodical to avoid excessive shedding of particles and organisms due to over-vigorous activity. Operators performing aseptic operations should adhere to strict aseptic technique at all times to prevent changes in air currents that introduce air of lower quality into the critical zone, Movement adjacent to the critical area should be restricted and the obstruction of the path of the unidirectional(first air) airflow should be avoided. ~~The ambient temperature and humidity should be set to prevent shedding due to operators becoming too cold (leading to excessive movement) or too hot.~~ Airflow visualisation studies should be considered as part of the operator's training programme.	7.18 Activities in clean areas that are not critical to the production processes should be kept to a minimum, especially when aseptic operations are in progress. Movement of personnel should be slow, controlled and methodical to avoid excessive shedding of particles and organisms due to over-vigorous activity. Operators performing aseptic operations should adhere to aseptic technique at all times to prevent changes in air currents that may introduce air of lower quality into the critical zone. Movement adjacent to the critical zone should be restricted and the obstruction of the path of the unidirectional (first air) airflow should be avoided. A review of airflow visualisation studies should be considered as part of the training programme.	**Processing** 73. Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

8 Production and Specific Technologies

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Terminally sterilized products	Terminally sterilised products	Terminally sterilised products
8.1 Preparation of components and ~~most products~~ materials should be ~~done~~ performed in at least a Grade D ~~environment~~ cleanroom in order to ~~give a low~~ limit the risk of microbial, pyrogen and particulate contamination, so that the product is suitable for ~~filtration and~~ sterilization. Where the product is at a high or unusual risk of microbial contamination~~, for example, because~~ (e.g. the product actively supports microbial growth ~~and/or,~~ the product must be held for ~~a~~ long periods before ~~sterilization and/or~~ filling or the product is not processed ~~mainly~~ mostly in closed vessels), then preparation should be carried out in a Grade C environment. Preparation of ointments, creams, suspensions and emulsions should be carried out in a Grade C environment before terminal sterilization.	8.1 Preparation of components and materials should be performed in at least a grade D cleanroom in order to limit the risk of microbial, endotoxin/pyrogen and particle contamination, so that the product is suitable for sterilisation. Where the product is at a high or unusual risk of microbial contamination (e.g. the product actively supports microbial growth, the product must be held for long periods before filling or the product is not processed mostly in closed vessels), then preparation should be carried out in at least a grade C environment. Preparation of ointments, creams, suspensions and emulsions should be carried out in at least a grade C environment before terminal sterilisation. Specific guidance regarding terminally sterilised veterinary medicinal products can be found within Annex 4 of the GMP guidelines.	28. Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where the product is at a high or unusual risk of microbial contamination, (for example, because the product actively supports microbial growth or must be held for a long period before sterilisation or is necessarily processed not mainly in closed vessels), then preparation should be carried out in a grade C environment. 30. Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilisation.
8.2 Primary packaging containers and components should be cleaned using validated processes to ensure that particulate, pyrogen and bioburden contamination is appropriately controlled.	8.2 Primary packaging containers and components should be cleaned using validated processes to ensure that particle, endotoxin/pyrogen and bioburden contamination is appropriately controlled.	N/A

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~~8.2~~ 8.3 Filling of products for terminal sterilization should be carried out in at least a Grade C environment.	8.3 Filling of products for terminal sterilisation should be carried out in at least a grade C environment.	29. Filling of products for terminal sterilisation should be carried out in at least a grade C environment.
~~8.3~~ 8.4 Where the product is at an unusual risk of contamination from the environment because, for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, ~~or the product is held for extended periods prior to terminal sterilization,~~ then the product should be filled in a Grade A zone with at least a Grade C background. ~~Preparation of ointments, creams, suspensions and emulsions should be carried out in a Grade C environment before terminal sterilization.~~	8.4 Where the CCS identifies that the product is at an unusual risk of contamination from the environment because, for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, then the product should be filled in grade A with at least a grade C background.	30. Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilisation.
~~8.4~~ 8.5 Processing of the bulk solution should include a filtration step with a microorganism retaining filter, where possible, to reduce bioburden levels and particulates prior to filling into the final product containers and there should be a maximum permissible time between preparation and filling.	8.5 Processing of the bulk solution should include a filtration step with a microorganism retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers and there should be a maximum permissible time between preparation and filling.	76. Where appropriate, measures should be taken to minimize the particulate contamination of the end product.
~~8.5~~ 8.6 Examples of operations to be carried out in the various grades are given in Table ~~3~~ 4. Table 4: Examples of operations and grades ~~they should be performed in~~ for terminally sterilized ~~products~~ preparation and processing operations A: Filling of products, when unusually at risk. C: Preparation of solutions, when unusually at risk. Filling of products. D: Preparation of solutions and components for subsequent filling.	8.6 Examples of operations to be carried out in the various grades are given in Table 3. Table 3: Examples of operations and grades for terminally sterilised preparation and processing operations **Grade A** - Filling of products, when unusually at risk. **Grade C** - Preparation of solutions, when unusually at risk. - Filling of products. **Grade D** - Preparation of solutions and components for subsequent filling.	Clean room and clean air device classification 17. Examples of operations to be carried out in the various grades are given in the table below (see also paragraphs 28 to 35):

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		<table><tr><th>Grade</th><th>Examples of operations for terminally sterilised products. (see paragra 30)</th></tr><tr><td>A</td><td>Filling of products, when unusually at risk</td></tr><tr><td>C</td><td>Preparation of solutions, when unusually at risk. Filling of products</td></tr><tr><td>D</td><td>Preparation of solutions and components for subsequent filling</td></tr></table> <table><tr><th>Grade</th><th>Examples of operations for aseptic preparations. (see paragraphs. 31-35)</th></tr><tr><td>A</td><td>Aseptic preparation and filling.</td></tr><tr><td>C</td><td>Preparation of solutions to be filtered.</td></tr><tr><td>D</td><td>Handling of components after washing.</td></tr></table>
Aseptic preparation and processing	Aseptic preparation and processing	Aseptic preparation
~~8.6~~ 8.7 Aseptic preparation and processing is the handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials and personnel are regulated to prevent ~~microbial contamination. Additional requirements apply to Restricted Access Barrier Systems (RABS) and isolators (refer clauses 5.15-5.22).~~ microbial, pyrogenic and particulate contamination.	转至 Glossary	N/A
~~8.7~~ 8.8 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's ~~contamination control strategy~~ CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. ~~Residual~~ Accepted residual risks should be ~~justified~~ formally documented.	8.7 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.	N/A
~~8.8~~ 8.9 Precautions to minimize microbial, ~~pyrogen~~ pyrogenic and particulate contamination should be taken, as per the site's ~~contamination control strategy~~ CCS, during the preparation of the aseptic environment, during all processing stages ~~,~~ (including the stages before and after bulk product sterilization), and until the product is sealed in its final container. The presence of materials liable to generate	8.8 Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilisation), and until the product is sealed in its final container. The presence of	64. Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.

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particulates and fibres should ~~not be permitted~~ be minimized in ~~clean areas~~ cleanrooms.	materials liable to generate particles and fibres should be minimized in cleanrooms.	
N/A	N/A	65. Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.
~~8.9~~ 8.10 Where possible, the use of equipment such as RABS, isolators or ~~closed~~ other systems, should be considered in order to reduce the need for critical interventions into the Grade A ~~environment~~ zone and to minimize the risk of contamination. ~~Automation~~ Robotics and automation of processes ~~should~~ can also be considered to ~~remove the risk of contamination by~~ eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, ~~SIP~~ sterilization in place).	8.9 Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, sterilisation in place).	N/A
~~8.10~~ 8.11 Examples of operations to be carried out in the various environmental grades are given in the Table 5. Table 5: Examples of operations and ~~which~~ grades ~~they should be performed in~~ for aseptic preparation and processing operations	8.10 Examples of operations to be carried out in the various environmental grades are given in Table 4. Table 4: Examples of operations and grades for aseptic preparation and processing operations	31~35

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<table><tr><td>Grade A</td><td>Critical zone for ● → ~~Critical processing zone.~~ ● → Aseptic assembly of filling equipment. ● → ~~Aseptic connections~~ Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilizing filter. These connections ~~(~~should be sterilized by steam-in-place whenever feasible~~)~~. ● → Aseptic compounding and mixing. ● → Replenishment of sterile bulk product, containers and closures. ● → Removal and cooling of unprotected (e.g. with no packaging) items from ~~heat~~ sterilizers. ● → Staging and conveying of sterile primary packaging components. ● → Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials~~, including interventions~~. ● → Loading ~~and unloading~~ of a lyophilizer.</td></tr><tr><td>Grade B</td><td>~~Direct support zone for the critical processing (grade A) zone~~ Background support for the Grade A zone (when not in an isolator). ● → Transport ~~and preparation of packaged equipment~~, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into the Grade A zone. ● → ~~Removal of sealed product from the grade A zone.~~</td></tr><tr><td>Grade C</td><td>● → Preparation of solutions to be filtered including weighing.</td></tr><tr><td>Grade D</td><td>● → Cleaning of equipment. ● → Handling of components, equipment and accessories after washing. ● → Assembly of cleaned components, equipment and accessories prior to be sterilized sterilization. ● → Assembly of closed and sterilized SUS using intrinsic aseptic connectors.</td></tr></table>	<table><tr><td>Grade A</td><td>- Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilised product contact surfaces are exposed) that are post the final sterilising grade filter. These connections should be sterilised by steam-in-place whenever possible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. - Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. - Loading of a lyophilizer.</td></tr><tr><td>Grade B</td><td>- Background support for grade A (when not in an isolator). - Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.</td></tr><tr><td>Grade C</td><td>- Preparation of solutions to be filtered including sampling and dispensing.</td></tr><tr><td>Grade D</td><td>- Cleaning of equipment. - Handling of components, equipment and accessories after cleaning. - Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation. - Assembly of closed and sterilised SUS using intrinsic sterile connection devices.</td></tr></table>	
8.12 For sterile products that cannot be filtered, the following should be considered: i. All product and component contact equipment should be sterilized prior to use. ii. All raw materials should be sterilized and aseptically added or subsequently sterilized by filtration. iii. Bulk solutions should be sterilized by a validated process, e.g. by heat, chemical sterilization or via sterile filtration. iv. All materials added to the sterile bulk product should be sterilized prior to addition.	8.11 For sterile products where the final formulation cannot be filtered, the following should be considered: i. All product and component contact equipment should be sterilised prior to use. ii. All raw materials or intermediates should be sterilised and aseptically added. iii. Bulk solutions or intermediates should be	31. Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background.

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	sterilised.	
~~8.11~~ 8.13 ~~Where the product is not subsequently sterile filtered, the preparation of equipment, components and ancillary items and products should be done in a grade A environment with a grade B background.~~ The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items and the preparation and filling of the sterile product should be treated as an aseptic process and performed in a Grade A zone with a Grade B background. Where an isolator or RABS is used, the background should be in accordance with paragraphs 4.21 & 4.22.	8.12 The unwrapping, assembly and preparation of sterilised equipment, components and ancillary items with direct or indirect product contact should be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the sterile product should be treated as an aseptic process and performed in grade A with a grade B background. Where an isolator is used, the background should be in accordance with paragraph 4.20.	33. Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.
~~8.12~~ 8.14 Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in a Grade A ~~environment~~ zone with a Grade B background~~,~~ when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilizing filter) or terminally sterilized. Where an isolator or RABS is used, the background should be in accordance with paragraphs 4.21 & 4.22.	8.13 Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in grade A with a grade B background when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilising grade filter) or terminally sterilised. Where an isolator or RABS is used, the background should be in accordance with paragraph 4.20.	32. Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background. 35. Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.
~~8.13~~ 8.15 ~~Unless subsequently sterilized by steam in place or conducted with validated intrinsic sterile connection devices,~~ Aseptic connections should be performed in a Grade A ~~environment~~ zone with a Grade B background ~~(or in an isolator with a suitable background),~~ unless subsequently sterilized in place or conducted with validated intrinsic sterile connection devices ~~in a way~~ that minimize~~s~~ ~~the~~ any potential contamination from the immediate environment~~, e.g. from~~	8.14 Aseptic connections should be performed in grade A with a grade B background unless subsequently sterilised in place or conducted with intrinsic sterile connection devices that minimize any potential contamination from the immediate environment. Intrinsic sterile connection devices should be designed to mitigate risk of contamination.	N/A

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~~operators or boundaries with lower grades~~. Where an isolator or RABS is used, the background should be in accordance with paragraphs 4.21 & 4.22. Aseptic connections~~, including those performed to replace equipment,~~ should be appropriately assessed and their effectiveness verified ~~as acceptable by process simulation tests~~. For requirements regarding intrinsic sterile connection devices ~~(refer clause 8.115)~~ refer to paragraph 8.120.	Where an isolator is used, the background should be in accordance with paragraph 4.20. Aseptic connections should be appropriately assessed and their effectiveness verified. For requirements regarding intrinsic sterile connection devices see paragraphs 8.129 and 8.130.	
~~8.14 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 Flow Work Stations, etc.) should ensure that the integrity of transfer system is maintained and the process of transfer should minimize the risk of contamination.~~		34. Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying should be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.
~~8.15~~ 8.16 Aseptic manipulations (including non-intrinsic aseptic connections) should be minimized ~~using~~ through the use of engineering design solutions such as ~~the use of~~ preassembled and sterilized equipment. Whenever feasible, product contact piping and equipment should be pre-assembled, ~~then cleaned~~ and sterilized in place. ~~The final sterile filtration should be carried out as close as possible to the filling point and downstream of aseptic connections wherever possible.~~	8.15 Aseptic manipulations (including non-intrinsic sterile connection devices) should be minimized through the use of engineering design solutions such as preassembled and sterilised equipment. Whenever feasible, product contact piping and equipment should be pre-assembled, and sterilised in place.	N/A
~~9.37~~ 8.17 There should be an ~~approved~~ authorized list of allowed interventions, both inherent and corrective, ~~which~~ that may occur during production ~~and in the APS~~. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be updated, as necessary to ensure consistency with the actual manufacturing activities. In	8.16 There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production (see paragraph 9.34). Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively	N/A

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the event that an unauthorized intervention is required, details of the intervention conducted should be recorded and fully assessed under the manufacturer's PQS.	minimized. The process of designing interventions should include the consideration of any impact on air-flows and critical surfaces and products. Engineering solutions should be used whenever possible to minimize incursion by operators during the intervention. Aseptic technique should be observed at all times, including the appropriate use of sterile tools for manipulations. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be first evaluated via risk management and APS and be kept up to date. Non-qualified interventions should only be used in exceptional circumstances, with due consideration of the risks associated with the intervention and with the authorisation of the quality unit. The details of the intervention conducted should be subject to risk assessment, recorded and fully investigated under the manufacturer's PQS. Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition.	
N/A	8.17 Interventions and stoppages should be recorded in the batch record. Each line stoppage or intervention should be sufficiently documented in batch records with the associated time, duration of the event, and operators involved (ref to paragraph 9.34).	N/A
~~8.16~~ 8.18 The duration of each aspect of ~~the aseptic manufacturing process~~ aseptic preparation and processing should be limited to a defined and validated maximum time, including:	8.18 The duration of each aspect of aseptic preparation and processing should be minimized and limited to a defined and validated maximum time, including:	78. The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilisation and use should be

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i. ~~a)~~ The holding time between equipment, component, and container cleaning, drying and sterilization. ii. ~~b)~~ The holding time for sterilized equipment, components, and containers ~~prior to~~ before use and during filling/assembly. iii. The holding time for a decontaminated environment, such as the RABS and isolator before and during filling /assembly. iv. ~~c)~~ The time between the start of the preparation of a ~~solution~~ product and its sterilization or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process. There should be a ~~set~~ maximum permissible time for each product that takes into account its composition and the prescribed method of storage. v. ~~e) Holding sterile~~ The holding time for sterilized product prior to filling. vi. ~~d) Aseptic assembly~~ The aseptic processing time. vii. ~~f)~~ The filling time. viii. ~~g)~~ The maximum exposure time of sterilized containers and closures in the critical processing zone (including filling) prior to closure.	i. The holding time between equipment, component, and container cleaning, drying and sterilisation. ii. The holding time for sterilised equipment, components, and containers before use and during filling/assembly. iii. The holding time for a decontaminated environment, such as the RABS or isolator before use. iv. The time between the start of the preparation of a product and its sterilisation or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process. There should be a maximum permissible time for each product that takes into account its composition and the prescribed method of storage. v. The holding time for sterilised product prior to filling. vi. The aseptic processing time. vii. The filling time.	minimised and subject to a time-limit appropriate to the storage conditions. 79. The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism-retaining filter should be minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.
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	8.19 Aseptic operations (including APS) should be observed on a regular basis by personnel with specific expertise in aseptic processing to verify the	N/A

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address inappropriate practices if detected.	correct performance of operations including operator behaviour in the cleanroom and address inappropriate practices if detected.	
Finishing of sterile products	Finishing of sterile products	Finishing of sterile products
~~8.17~~ 8.20 Open primary packaging containers (including partially stoppered vials or prefilled syringes) should be maintained under Grade A conditions ~~(e.g. use of isolator technology, grade A with B background, with physical segregation from operators)~~ with Grade B background (e.g. Barrier Technology), ~~or grade A LAF carts (with suitable grade B background environment and~~ or under Grade A conditions with physical segregation from operators (e.g. UDAF carts) ~~at all times~~ until the stopper is fully inserted.	8.20 Open primary packaging containers should be maintained under grade A conditions with the appropriate background for the technology as described in paragraph 4.20. For partially stoppered vials or prefilled syringes (see paragraph 8.126).	116. Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.
8.21 的第一句	8.21 Final containers should be closed by appropriately validated methods.	117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.
~~8.18~~ 8.21 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. Blow-fill-seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, should be subject to 100% integrity testing. Samples of ~~other~~ containers closed by other methods should be taken and checked for integrity ~~utilising~~ using 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~~ scientifically valid sampling plan should be utilized. The sample size should be	8.22 Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small volume containers (≤100 ml) closed by fusion should be subject to 100% integrity testing using validated methods. For large volume containers (>100 ml) closed by fusion, reduced	117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

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based on information such as supplier approval, packaging component specifications and process knowledge. It should be noted that visual inspection alone is not considered as an acceptable integrity test method.	sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. It should be noted that visual inspection is not considered as an acceptable integrity test method.	
8.21 的后半段	8.23 Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier management, packaging component specifications and process knowledge.	117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.
~~8.19~~ 8.22 Containers sealed under vacuum (where the vacuum is necessary for the product stability) should be tested for maintenance of vacuum after an appropriate~~,~~ pre-determined period and during shelf life.	8.24 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate pre-determined period prior to certification/release and during shelf life.	123. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.
~~8.20~~ 8.23 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or temperature extremes).	8.25 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or extreme temperatures).	N/A
~~8.21~~ 8.24 ~~As~~ Where the equipment used to crimp vial caps can generate large quantities of non-viable particulates, measures to prevent particulate contamination such as locating the equipment ~~should be located~~ at a physically separate station equipped with adequate air extraction should be taken.	8.26 Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures to prevent particle contamination such as locating the equipment at a physically separate station equipped with adequate air extraction should be taken.	119. As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.
~~8.22~~ 8.25 Vial capping can be undertaken as an aseptic	8.27 Vial capping of aseptically filled products can be	118. The container closure system for

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process using sterilized caps or as a clean process outside the aseptic core. Where ~~this~~ the latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped. Where capping is a manual process it should be performed ~~in~~ under Grade A conditions either in an appropriately designed isolator or into Grade A zone with a Grade B background.	undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic processing area. Where the latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped. The supporting background environment of grade A air supply should meet at least grade D requirements. Where capping is a manual process, it should be performed under grade A conditions either in an appropriately designed isolator or in grade A with a grade B background.	aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion. 120. Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped.
~~8.23~~ 8.26 ~~In the case where capping~~ Where capping of aseptically filled sterile product is conducted as a clean process with Grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place. ~~Microbial ingress studies (or alternative methods) should be utilized to determine the acceptable stopper height displacement.~~	8.28 Where capping of aseptically filled sterile product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place.	121. Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination.
~~8.24~~ 8.27 Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize microbial contamination.	8.29 Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize contamination. RABS and isolators may be beneficial in assuring the required conditions.	121. Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimise microbial contamination.
~~8.25~~ 8.28 RABS and isolators may be beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions into	转至 8.29	122. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human

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the capping operation.		interventions into the capping operation.
~~8.26~~ 8.29 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.~~ Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, ~~to~~ the potential impact ~~to the patient~~ of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analyzed. Batches with unusual levels of defects, when compared with routine defect ~~levels~~ numbers for the process (based on historical and trend data), should lead to an investigation ~~and consideration of partial or the whole rejection of the batch concerned~~. A defect library should be generated and maintained which captures all known classes of defects. The defect library ~~can~~ should be used ~~as a training tool for~~ for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified should trigger an investigation as it indicates a possible failure of the original inspection process.	8.30 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on routine and trend data), should be investigated. A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified subsequently should trigger an investigation as it indicates a possible failure of the original inspection process.	N/A
~~8.27~~ 8.30 When inspection is done manually, it should be ~~done~~ performed under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately ~~validated~~ controlled and qualified. Operators performing the inspection should undergo ~~robust~~ visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate ~~sample~~ samples from	8.31 When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be	124. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if

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the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system~~)~~, ~~component~~ container size or fatigue at the end of shift) and should include consideration of eyesight checks. Operator distractions should be ~~removed~~ minimized and frequent breaks, of an appropriate duration, from inspection should be taken.	undertaken using appropriate samples from the manufacturer's defect library sets and taking into 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) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, should be taken from inspection.	worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.
~~8.28~~ 8.31 Where automated methods of inspection are used, the process should be validated to detect known defects ~~with sensitivity~~ (which may impact the product quality, safety or efficacy) and be equal to, or better than, manual inspection methods. ~~And~~ The performance of the equipment ~~checked~~ should be challenged using representative defects prior to start up and at regular intervals.	8.32 Where automated methods of inspection are used, the process should be validated to detect known defects (which may impact product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch.	N/A
~~8.29~~ 8.32 Results of the inspection should be recorded and defect types and ~~levels~~ numbers trended. Reject ~~rates~~ levels for the various defect types should also be trended based on statistical principles. ~~Investigations should be performed as appropriate to address adverse trends or discovery of new defect types.~~ Impact to product on the market should be assessed as part of ~~this~~ the investigation when adverse trends are observed.	8.33 Results of the inspection should be recorded and defect types and numbers trended. Reject levels for the various defect types should also be trended based on statistical principles. Impact to product on the market should be assessed as part of the investigation when adverse trends are observed.	N/A
Sterilization	Sterilisation	Sterilisation
~~8.30~~ 8.33 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~~ sterile filtration process and/or aseptic processing. Where it is not	8.34 Where possible, finished product should be terminally sterilised, using a validated and controlled sterilisation process, as this provides a greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing.	N/A

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possible for a product to undergo ~~a~~ terminal sterilization, consideration should be given to using terminal bioburden reduction steps, such as heat treatments (e.g. pasteurization), combined with aseptic ~~processing~~ process to give improved sterility assurance.	Where it is not possible for a product to undergo terminal sterilisation, consideration should be given to using post-aseptic processing terminal heat treatment, combined with aseptic process to give improved sterility assurance.	
~~8.31~~ 8.34 The selection, design and location of the equipment and cycle/programme used for sterilization should be ~~decided using QRM principles~~ based on scientific principles and data which demonstrate repeatability and reliability of the sterilization process. Critical parameters should be defined, controlled, monitored and recorded.	8.35 The selection, design and location of the equipment and cycle/programme used for sterilisation should be based on scientific principles and data which demonstrate repeatability and reliability of the sterilisation process. All parameters should be defined, and where critical, these should be controlled, monitored and recorded.	N/A
~~8.33 8.34 8.36~~ 8.35 All sterilization processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilized and its sterilization. Before any sterilization process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilizing conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by biological indicators (BI) ~~where appropriate~~. For effective sterilization, the whole of the ~~material~~ product, and surfaces of equipment and components ~~must~~ should be subject~~ed~~ to the required treatment and the process should be designed to ensure that this is achieved.	8.36 All sterilisation processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilised and its sterilisation. Before any sterilisation process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilising conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by Biological Indicators (BI). For effective sterilisation, the whole of the product, and surfaces of equipment and components should be subject to the required treatment and the process should be designed to ensure that this is achieved.	83. All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.
		84. Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled

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		intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.
		85. For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.
~~8.33~~ 8.36 Particular attention should be given when the adopted sterilization method is not described in the current edition of the Pharmacopoeia, or when it is used for a product which is not a simple aqueous solution. Where possible, heat sterilization is the method of choice. ~~Regardless, the sterilization process must be in accordance with the registered marketing and manufacturing specifications.~~	8.37 Particular attention should be given when the adopted product sterilisation method is not described in the current edition of the Pharmacopoeia, or when it is used for a product which is not a simple aqueous solution. Where possible, heat sterilisation is the method of choice.	83. All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.
8.37 Validated loading patterns should be established for all sterilization processes and should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.	8.38 Validated loading patterns should be established for all sterilisation processes and load patterns should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.	N/A
~~8.35~~ 8.38 The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk~~, with a minimum of at least annually~~. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually. ~~Revalidation of the sterilization process should be conducted whenever significant modifications have been made to the product, product packaging, sterilization load~~	8.39 The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.	84. Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of

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~~configuration, sterilizing equipment or sterilization process parameters.~~		the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.
~~8.37~~ 8.39 Routine operating parameters should be established and adhered to for all sterilization processes, e.g. physical parameters and loading patterns~~, etc~~.	8.40 Routine operating parameters should be established and adhered to for all sterilisation processes, e.g. physical parameters and loading patterns.	86. Validated loading patterns should be established for all sterilisation processes.
~~8.32~~ 8.40 There should be mechanisms in place to detect a sterilization cycle that does not conform to the validated parameters. Any failed sterilization or ~~atypical sterilization cycles~~ sterilization that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) ~~must~~ should be ~~formally~~ investigated.	8.41 There should be mechanisms in place to detect a sterilisation cycle that does not conform to the validated parameters. Any failed sterilisation or sterilisation that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) should be investigated.	N/A
~~8.38~~ 8.41 Suitable ~~biological indicators (BIs)~~ BIs placed at appropriate locations may be considered as an additional method ~~for monitoring~~ to support the validation of the sterilization process. BIs should be stored and used according to the manufacturer's instructions. ~~Prior to use of a new batch/lot of BIs, the quality of the batch/lot should be verified by confirming the viable spore count and identity.~~ Where BIs are used to ~~validate~~ support validation and/or to monitor a sterilization process (e.g. for ethylene oxide), positive controls should be tested for each sterilization cycle~~, with strict precautions in place to avoid transferring microbial contamination from BIs, including preventing positive control BIs from contaminating BIs exposed to the sterilization cycle~~. If BIs are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. BI results in isolation do not give	8.42 Suitable BIs placed at appropriate locations should be considered as an additional method to support the validation of the sterilisation process. BIs should be stored and used according to the manufacturer's instructions. Where BIs are used to support validation and/or to monitor a sterilisation process (e.g. with ethylene oxide), positive controls should be tested for each sterilisation cycle. If BIs are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. BI results in isolation should not be used to override other critical parameters and process design elements.	87. Biological indicators should be considered as an additional method for monitoring the sterilisation. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

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assurance of sterilization and should not be used to override other critical parameters and process design elements.		
8.42 The reliability of BIs is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that BI quality is not compromised. Prior to use of a new batch/lot of BIs, the population and identity of the indicator organism of the batch/lot should be verified. For other critical parameters, e.g. D-value, Z- value, the batch certificate provided by the qualified supplier can normally be used.	8.43 The reliability of BIs is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that BI quality is not compromised. Prior to use of a new batch/lot of BIs, the population, purity and identity of the indicator organism of the batch/lot should be verified. For other critical parameters, e.g. D-value, Z-value, the batch certificate provided by the qualified supplier can normally be used.	N/A
~~8.39~~ 8.43 There should be a clear means of differentiating products, equipment and components, which have not been ~~sterilized~~ subjected to the sterilization process from those which have. ~~Each basket, tray or other carrier of products,~~ Containers used to carry products such as baskets or trays, items of equipment and/or components should be clearly labelled (or electronically tracked) with the material name, ~~its~~ product batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape, or irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process. However, these indicators show only that the sterilization process has occurred, they do not ~~necessarily~~ indicate product sterility or achievement of the required sterility assurance level.	8.44 There should be a clear means of differentiating products, equipment and components, which have not been subjected to the sterilisation process from those which have. Equipment such as baskets or trays used to carry products, other items of equipment and/or components should be clearly labelled (or electronically tracked) with the product name and batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape, or irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch material, component, equipment) has passed through a sterilisation process. However, these indicators show only that the sterilisation process has occurred; they do not indicate product sterility or achievement of the required sterility assurance level.	88. There should be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.
~~8.40~~ 8.44 Sterilization records should be available for each sterilization run. Each cycle should have a unique identifier. They should be reviewed and approved as part of the batch	8.45 Sterilisation records should be available for each sterilisation run. Each cycle should have a unique identifier. Their conformity should be reviewed and	89. Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release

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~~release~~ certification procedure.	approved as part of the batch certification/release procedure.	procedure.
~~8.41~~ 8.45 Where possible, materials, equipment and components should be sterilized by validated methods appropriate to the specific material. Suitable protection after sterilization should be provided to prevent recontamination. If ~~items sterilized "in house"~~ sterilized items are not used immediately after sterilization, these should be stored using appropriately sealed packaging. ~~in at least a grade B environment,~~ A maximum hold ~~period~~ time should also be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in ~~grade B (where justified)~~ a cleanroom if the integrity and configuration ~~(e.g. multiple sterile coverings that can be removed at each transfer from lower to higher grade)~~ of the sterile pack allows the items to be readily disinfected during transfer by operators into the Grade A zone, (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilization.	8.46 Where required, materials, equipment and components should be sterilised by validated methods appropriate to the specific material. Suitable protection after sterilisation should be provided to prevent recontamination. If sterilised items are not used immediately after sterilisation, these should be stored using appropriately sealed packaging and a maximum hold time should be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilisation.	N/A
~~8.42 Transfer of materials, equipment, and components into an aseptic processing area should be via a unidirectional process (e.g. through a double-door autoclave, a depyrogenation oven, effective transfer disinfection, or, for gaseous or liquid materials, a bacteria-retentive filter).~~	转至 4.11	Processing 81. Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters

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~~8.43~~ 8.46 Where materials, equipment, ~~and~~ components and ancillary items are sterilized in sealed packaging and then transferred into the Grade A~~/B area~~ zone, this should be done using appropriate, validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to ~~be effective in not posing an unacceptable~~ effectively control the potential risk of contamination of the Grade A ~~/~~zone and Grade B area and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the ~~grade A/B area~~ Grade B and Grade A areas. ~~Packaging may be multi layered to allow removal of a single layer at each interface to a higher grade.~~	8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.	N/A
~~8.44~~ 8.47 Where materials, equipment, components and ancillary items are sterilized in sealed packaging or containers, ~~the integrity of the sterile protective barrier should be qualified for the maximum hold time, and the process should include inspection of each sterile item prior to its use to ensure that the sterile protective measures have remained integral.~~ the packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system and the maximum hold time before sterilization and maximum shelf life assigned to the sterilized items. The integrity of the sterile protective barrier system for each of the sterilized items should be confirmed prior to use.	8.48 Where materials, equipment, components and ancillary items are sterilised in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilisation and the maximum shelf life assigned to the sterilised items. The integrity of the sterile protective barrier system for each of the sterilised items should be checked prior to use.	N/A
~~8.45~~ 8.48 For materials, equipment, components and ancillary items that are necessary for aseptic processing but cannot be sterilized, an effective and validated disinfection and transfer	8.49 For materials, equipment, components and ancillary items that are not a direct or indirect product contact part and are necessary for aseptic processing	Processing 77. Components, containers and equipment should be handled after the final cleaning

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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.	but cannot be sterilised, 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 programme.	process in such a way that they are not recontaminated.
Sterilization by heat	Sterilisation by heat	Sterilisation by heat
8.49 Each heat sterilization cycle should be recorded ~~on a time/temperature chart with a sufficiently large scale or by other appropriate equipment~~ 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).	8.50 Each heat sterilisation cycle should be recorded either electronically or by hardcopy, using equipment with suitable accuracy and precision. The system should 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 (e.g. by the use of duplex/double probes connected to independent control and monitoring systems).	90. Each heat sterilisation cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.
8.50 The position of the temperature probes used for controlling and/or recording should be determined during the validation ~~(~~which should include heat distribution and penetration studies~~)~~ and, where applicable, also checked against a second independent temperature probe located at the same position.	8.51 The position of the temperature probes used for controlling and/or recording should be determined during the validation and selected based on system design and in order to correctly record and represent routine cycle conditions. Validation studies should be designed to demonstrate the suitability of system control and recording probe locations, and should include the verification of the function and location of these probes by the use of an independent monitoring probe located at the same position during validation.	90. Each heat sterilisation cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.
~~8.51 Chemical or biological indicators may also be used, but~~	N/A	91. Chemical or biological indicators may

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~~should not take the place of physical measurements.~~		also be used, but should not take the place of physical measurements.
~~8.52~~ 8.51 Sufficient time ~~must~~ should be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period ~~is commenced~~ starts. ~~This time must be determined for each type of load to be processed.~~ For sterilization cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring the load probe temperature is controlled within defined temperature range prior to cycle commencement.	8.52 The whole of the load should reach the required temperature before measurement of the sterilising time-period starts. For sterilisation cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring the load probe temperature is controlled within defined temperature range prior to cycle commencement.	92. Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.
~~8.53~~ 8.52 After completion of the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling ~~fluid~~ liquid or gas that comes in contact with the product or sterilized material should be sterilized ~~unless it can be shown that any leaking container would not be approved for use~~.	8.53 After completion of the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilised material should be sterilised.	93. After the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised unless it can be shown that any leaking container would not be approved for use.
~~8.48~~ 8.53 In those cases where parametric release has been authorized, a robust system should be applied to the product lifecycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed. Further guidance regarding parametric release is provided in Annex 17.	8.54 In those cases where parametric release has been authorized, a robust system should be applied to the product lifecycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed. Further guidance regarding parametric release is provided in Annex 17.	N/A
Moist heat sterilization	Moist heat sterilisation	Moist heat
~~8.47~~ 8.54 Moist heat sterilization utilises ~~clean~~ steam or superheated water, typically at lower temperatures and shorter duration than dry heat processes, in order to sterilize a product or article. Moist heat sterilization of hard goods or porous loads	8.55 Moist heat sterilisation can be achieved using steam, (direct or indirect contact), but also includes other systems such as superheated water systems (cascade or immersion cycles) that could be used for	N/A

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is primarily effected by latent heat of condensation of clean steam and the quality of steam is therefore important to provide consistent results. For aqueous liquid-filled containers, energy from moist heat is transferred through conduction and/or convection to the content of the container without direct contact with the autoclave steam. In these cases, time and temperature are the key parameters and steam quality does not have the same impact to the process. ~~The reduced level of moisture in dry heat sterilization process reduces heat penetration which is primarily effected by conduction. Dry heat processes may be utilized to sterilize or control bioburden of thermally stable materials and articles. Dry heat sterilization is of particular use in the removal of thermally robust contaminants such as pyrogens and is often utilized in the preparation of aseptic filling components.~~ Moist heat sterilization processes may be utilized to sterilize or control bioburden (for non- sterile applications) of thermally stable materials, articles or products and is the preferred method of sterilization, where possible. Moist heat sterilization can be achieved using steam, (direct or indirect contact), but also includes other systems such as superheated water systems. Superheated systems are typically used for the terminal sterilization of product in flexible containers where the pressure differentials associated with the steam would cause damage to the primary container.	containers that may be damaged by other cycle designs (e.g. Blow-Fill-Seal containers, plastic bags).	
8.60	8.56 The items to be sterilised, other than products in sealed containers, should be dry, packaged in a protective barrier system which allows removal of air and penetration of steam and prevents recontamination after sterilisation. All loaded items should be dry upon removal from the steriliser. Load	95. The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with

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	dryness should be confirmed by visual inspection as a part of the sterilisation process acceptance.	the sterilizing agent at the required temperature for the required time.
~~8.54~~ 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, ~~seal and~~ packaging material integrity and moisture on removal from the autoclave. ~~Seal and packaging integrity should also be inspected immediately prior to use.~~ Any item~~s~~ found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.	8.57 For porous cycles (hard goods), time, temperature and pressure should be used to monitor the process and be recorded. Each sterilised item should be inspected for damage, packaging material integrity and moisture on removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.	94. Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.
~~8.55 System and cycle faults should be registered and recorded by the control and monitoring system and appropriate actions taken prior to release of the process.~~	N/A	
8.56 For ~~sterilizers~~ autoclaves fitted with a drain at the bottom of the chamber, ~~it may also be necessary to record the temperature~~ the temperature should be recorded at this position throughout the sterilization period. For ~~Steam In-Place (SIP)~~ steam in place systems, ~~it may also be necessary to record~~ the temperature should be recorded at condensate drain locations throughout the sterilization period.	8.58 For autoclaves capable of performing prevacuum sterilisation cycles, the temperature should be recorded at the chamber drain throughout the sterilisation period. Load probes may also be used where appropriate but the controlling system should remain related to the load validation. For steam in place systems, the temperature should be recorded at appropriate condensate drain locations throughout the sterilisation period.	
8.57 Validation of porous cycles should include a ~~consideration~~ calculation of equilibration time, exposure time, correlation of pressure and temperature and maximum temperature range during exposure. Validation of fluid ~~for porous~~ cycles ~~and~~ should include temperature, time and/or F_0 ~~for fluid cycles~~. These critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilization validation and routine cycle acceptance criteria. ~~Revalidation should be performed~~	8.59 Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature and the minimum/maximum temperature range during exposure. Validation of fluid cycles should include temperature, time and/or F_0. Critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilisation validation and routine cycle	N/A

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~~annually.~~	acceptance criteria.	
8.58 ~~There should be frequent~~ Leak tests on the sterilizing system ~~to~~ should be ~~sterilized~~ carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilization, to a pressure ~~equivalent to or~~ lower than the environment surrounding the sterilized system. ~~The frequency of testing should be based on the principles of QRM.~~	8.60 Leak tests on the steriliser should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilisation, to a pressure lower than the environment surrounding the steriliser.	N/A
8.59 ~~When the sterilization process includes air purging (e.g. porous autoclave loads, lyophilizer chambers)~~ 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 condensate.	8.61 There should be adequate assurance of air removal prior to and during sterilisation when the sterilisation 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 the use of an air detector system. Loads to be sterilised should be designed to support effective air removal and be free draining to prevent the build-up of condensate.	N/A
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 ~~but which~~ and prevents recontamination after sterilization. All loaded items should be dry upon removal from the sterilizer. Load dryness should be confirmed by visual inspection as a part of the sterilization process acceptance.	转至 8.56	95. The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilizing agent at the required temperature for the required time.
8.61 If it is necessary to wet equipment using WFI (e.g. ultrafiltration membrane) prior to the sterilization process, then a risk-based assessment should be carried out to demonstrate the acceptable dryness level that will not impact the sterility of the equipment sterilized and the product sterility assurance		N/A

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level. The hold time between the wetting phase and sterilization should be justified and validated.		
~~8.61~~ 8.62 Distortion and damage of ~~flexible~~ non-rigid containers that are terminally sterilized, such as containers produced by Blow-Fill-Seal or Form-Fill-Seal ~~technology~~ technologies, should be prevented by appropriate cycle design and control (for instance setting correct ~~counter~~ pressure, heating and cooling rates and loading patterns).	8.62 Distortion and damage of non-rigid containers that are terminally sterilised, such as containers produced by Blow-Fill-Seal or Form-Fill-Seal technologies, should be prevented by appropriate cycle design and control (for instance setting correct pressure, heating and cooling rates and loading patterns).	N/A
~~8.62 Care should be taken to ensure that materials or equipment are not contaminated after the sterilization exposure phase of the cycle due to the introduction of non-sterile air into the chamber during subsequent phases; typically only sterile filtered air would be introduced into the chamber during these phases.~~		N/A
8.63 Where ~~sterilization in place (SIP)~~ steam in place systems are used (~~for example~~ e.g. for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to assure all parts of the system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate ~~critical~~ locations during routine use~~, this is~~ to ensure all areas are effectively and reproducibly sterilized. These ~~critical~~ locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilized by ~~SIP~~ steam in place it should remain integral and held under positive pressure prior to use~~, the maximum duration of the hold time should be qualified~~.	8.63 Where steam in place systems are used for sterilisation (e.g. for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to assure all parts of the 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 sterilised. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilised by steam in place, it should remain integral and where operations require, maintained under positive pressure or otherwise equipped with a sterilising vent filter prior	N/A

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	to use.	
8.64 For systems using superheated water rather than steam, as the sterilizing agent, the heated water should consistently reach all of the required contact points. Initial qualification studies should include temperature mapping of the entire load. There should be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.	8.64 In fluids load cycles where superheated water is used as the heat transfer medium, the heated water should consistently reach all of the required contact points. Initial qualification studies should include temperature mapping of the entire load. There should be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.	N/A
8.65 For the qualification of superheated systems it should be demonstrated that all parts of the load meet the minimum required temperature and that routine monitoring probes are located in the worst case positions identified during the qualification process.	8.65 Validation of the sterilisation of fluids loads in a superheated water autoclave should include temperature mapping of the entire load and heat penetration and reproducibility studies. All parts of the load should heat up uniformly and achieve the desired temperature for the specified time. Routine temperature monitoring probes should be correlated to the worst case positions identified during the qualification process.	N/A
Dry heat sterilization	Dry heat sterilisation	Dry heat
~~8.64~~ 8.66 Dry heat sterilization is of particular use in the removal of thermally robust contaminants such as pyrogens and is often ~~utilized~~ used in the preparation of components for aseptic filling ~~components~~. The combination of time and temperature to which product, components and equipment are exposed should produce an adequate and reproducible level of lethality and/or pyrogen (endotoxin) inactivation/removal when operated routinely within the established ~~tolerances~~ limits.	8.66 Dry heat sterilisation utilizes high temperatures of air or gas to sterilise a product or article. Dry heat sterilisation is of particular use in the thermal removal of difficult-to-eliminate thermally robust contaminants such as endotoxin/pyrogen and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components or equipment are exposed should produce an adequate and reproducible level of lethality and/or endotoxin/pyrogen inactivation/removal when operated routinely within the established limits. The process may be operated	97. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

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	in an oven or in a continuous tunnel process, e.g. for sterilisation and depyrogenation of glass containers.	
~~8.65~~ 8.67 Dry heat sterilization ~~or~~ /depyrogenation tunnels ~~are typically employed to prepare components for aseptic filling operations but may be used for other processes. Tunnels should be configured to ensure that airflow patterns protect the integrity and performance of the~~ should be configured to ensure that airflow protects the integrity and performance of the Grade A sterilizing zone~~,~~ by maintaining ~~a stable~~ pressure differentials and airflow ~~pattern~~ through the tunnel from the higher grade area to the lower grade area. ~~All air supplied to the tunnel should pass through a HEPA filter; periodic tests should be performed to demonstrate filter integrity.~~ 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. 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 (at least biannually). Any tunnel parts that come into contact with sterilized components should be appropriately sterilized or disinfected. Critical process parameters that should be considered during validation and/or routine processing should include, but may not be limited to: i. Belt speed or dwell time within the sterilizing zone. ii. Temperature – minimum and maximum temperatures. iii. Heat penetration of the material/article. iv. Heat distribution/uniformity. v. Airflows – correlated with the heat distribution and penetration studies.	8.67 Dry heat sterilisation/depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the grade A sterilising zone by maintaining appropriate pressure differentials and airflow through the tunnel. Air pressure difference profiles should be assessed. The impact of any airflow change should be assessed to ensure the heating profile is maintained. All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests (at least biannually) should be performed to demonstrate air filter integrity. Any tunnel parts that come into contact with sterilised components should be appropriately sterilised or disinfected. Critical process parameters that should be considered during validation and/or routine processing should include, but are not limited to: i. Belt speed or dwell time within the sterilising zone. ii. Temperature – minimum and maximum temperatures. iii. Heat penetration of the material/article. iv. Heat distribution/uniformity. v. Airflows determined by air pressure difference profiles correlated with the heat distribution and	97. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

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	penetration studies.	
~~8.46~~ 8.68 When a thermal depyrogenation process is used for any component~~s~~ or product contact equipment, validation studies should be performed to demonstrate that the process provides a suitable F_h value and results ~~will result~~ in a minimum 3 log reduction in endotoxins concentration. ~~There is no additional requirement to demonstrate sterilization in these cases.~~	8.68 When a thermal process is used as part of the depyrogenation process for any component or product contact equipment/material, validation studies should be performed to demonstrate that the process provides a suitable F_h value and results in a minimum 3 log_{10} reduction in endotoxin concentration. When this is attained, there is no additional requirement to demonstrate sterilisation in these cases.	N/A
~~8.66~~ 8.69 ~~When using endotoxin spiked containers these need to~~ Containers inoculated with endotoxin should be used during validation and should be carefully managed with a full reconciliation performed. Containers should be representative of the materials normally processed. Endotoxin quantification and recovery efficiency should also be demonstrated through biological measurement.	8.69 Containers spiked with endotoxin should be used during validation and should be carefully managed with a full reconciliation performed. Containers should be representative of the materials normally processed (in respect to composition of the packaging materials, porosity, dimensions, nominal volume). Endotoxin quantification and recovery efficiency should also be demonstrated.	N/A
~~8.67~~ 8.70 Dry heat ovens are typically employed to sterilize or depyrogenate primary packaging components, finished materials or ~~APIs~~ active substances but may be used for other processes. They should be maintained at a positive pressure relative to lower grade areas throughout the sterilization and post sterilization hold process. All air entering the oven should pass through a ~~HEPA~~ sterilizing filter. Critical process parameters that should be considered in ~~validation~~ qualification and/or routine processing should include, but may not be limited to: i. ~~a)~~ Temperature. ii. ~~b)~~ Exposure period/time. iii. ~~c)~~ Chamber pressure (for maintenance of over pressure).	8.70 Dry heat ovens are typically employed to sterilise or depyrogenate primary packaging components, starting materials or active substances but may be used for other processes. They should be maintained at a positive pressure relative to lower grade clean areas throughout the sterilisation and post sterilisation hold process unless the integrity of the packaging is maintained. All air entering the oven should pass through a HEPA filter. Critical process parameters that should be considered in qualification and/or routine processing should include, but are not limited to:	N/A

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iv. Air speed. v. Air quality within the oven. vi. ~~d)~~ Heat penetration of material/article (slow to heat spots ~~and different loads~~). vii. ~~e)~~ Heat distribution/uniformity.	i. Temperature. ii. Exposure period/time. iii. Chamber pressure (for maintenance of over pressure). iv. Air speed. v. Air quality within the oven. vi. Heat penetration of material/article (slow to heat spots). vii. Heat distribution/uniformity. viii. Load pattern and configuration of articles to be sterilised/depyrogenated including minimum and maximum loads.	
~~8.68~~ 8.71 For dry heat sterilization of starting materials and intermediates, the same principles should be applied. Consideration should also be given to factors affecting heat penetration such as the container type, size and packing matrix.		N/A
Sterilization by radiation	Sterilisation by radiation	Sterilisation by radiation
~~8.69~~ 8.72 Guidance regarding ionising radiation sterilization can be found within Annex 12 ~~of the EU GMP~~.	8.71 Sterilisation by radiation is used mainly for the sterilisation of heat sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilisation. Guidance regarding ionising radiation sterilisation can be found within Annex 12.	98. Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on
~~8.70~~ 8.73 ~~Radiation sterilization~~ Sterilization by radiation is used mainly for the sterilization of heat sensitive materials and products. ~~Many medicinal products and some packaging materials are radiation sensitive, so this method is permissible~~		

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~~only when the absence of deleterious effects on the product has been confirmed.~~ Ultraviolet irradiation is not ~~normally~~ an acceptable method of sterilization.		the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.
N/A		99. During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.
N/A		100. Biological indicators may be used as an additional control
~~8.71~~ 8.74 Validation procedures should ensure that the effects of variations in density of the product and packages are considered.	8.72 Validation procedures should ensure that the effects of variation in density of the product and packages are considered.	101. Validation procedures should ensure that the effects of variations in density of the packages are considered.
N/A		102. Materials handling procedures should prevent mix-up between irradiated and nonirradiated materials. Radiation sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not.
N/A		103. The total radiation dose should be

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		administered within a predetermined time span.
Sterilization with ethylene oxide	Sterilisation with ethylene oxide	Sterilisation with ethylene oxide
~~8.72~~ 8.75 This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing ~~to reduce~~ result in the reduction of any residual ethylene oxide (EO) gas and reaction products to defined acceptable limits for the ~~type~~ given product or material.	8.73 This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing result in the reduction of any residual ethylene oxide (EO) gas and reaction products to defined acceptable limits for the given product or material.	104. This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.
~~8.73~~ 8.76 Direct contact between gas and microbial cells is essential, precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature, porosity and quantity of packaging materials can significantly affect the process.	8.74 Direct contact between gas and microbial cells is essential, precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature, porosity and quantity of packaging materials can significantly affect the process.	105. Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.
~~8.74~~ 8.77 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.	8.75 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. Where steam is used to condition the load for sterilisation, it should be of an appropriate quality. The time required for this should be balanced against the opposing need to minimize the time before sterilisation.	106. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilisation.
~~8.75~~ 8.78 Each sterilization cycle should be monitored with suitable ~~biological indicators~~ BIs, using the appropriate number of test ~~pieces~~ units distributed throughout the load at defined locations that have been shown to be worst case during validation ~~unless parametric release has been~~	8.76 Each sterilisation cycle should be monitored with suitable BIs, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst case locations during validation.	107. Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of

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~~authorized by the National Competent Authority~~.		the batch record.
~~8.76~~ 8.79 Critical process variables that could be considered as part of the sterilization process validation and routine monitoring include, but are not limited to ~~EO gas concentration, relative humidity, temperature and EO gas pressure and exposure time~~: i. EO gas concentration. ii. EO gas pressure. iii. Amount of EO gas used. iv. Relative humidity. v. Temperature. vi. Exposure time.	8.77 Critical process parameters that could be considered as part of the sterilisation process validation and routine monitoring include, but are not limited to: i. EO gas concentration. ii. Pressure. iii. Amount of EO gas used. iv. Relative humidity. v. Temperature. vi. Exposure time.	108. For each sterilisation cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.
~~8.77~~ 8.80 After sterilization, the load should be aerated to allow EO gas and/or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a sterilizer chamber and/or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall EO sterilization process validation.	8.78 After sterilisation, the load should be aerated to allow EO gas and/or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a steriliser chamber and/or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall EO sterilisation process validation.	109. After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.
~~Filtration~~ Filter sterilization of ~~medicinal~~ products which cannot be sterilized in their final container	Filter sterilisation of products which cannot be sterilised in their final container	Filtration of medicinal products which cannot be sterilised in their final container
8.~~78~~81 If ~~a liquid~~the product cannot be ~~terminally~~ sterilized ~~by a microbiocidal process, it~~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 ~~micron~~ µm (or less) ~~or with at least equivalent micro-organism~~	8.79 If the product cannot be sterilised in its final container, solutions or liquids should be sterilised by filtration through a sterile sterilising grade filter (with a nominal pore size of a maximum of 0.22 µm that has been appropriately validated to obtain a sterile	110. Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be

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~~retaining properties),~~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~~, see~~ and as described in the marketing authorization (refer to paragraph 8.~~119.~~125).	filtrate) and subsequently aseptically filled into a previously sterilised container. The selection of the filter used should ensure that it is compatible with the product and as described in the marketing authorization (see paragraph 8.135).	sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.
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 ~~sterilizing~~ sterile filtration process, as compared ~~to~~ with other sterilization processes, a second filtration through a sterile~~, sterilising~~ sterilizing grade filter ~~(positioned as per clause 8.15)~~ immediately prior to filling~~, is advisable~~ should be considered as part of an overall CCS.	8.80 Suitable bioburden reduction prefilters and/or sterilising 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 final sterilising filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilisation processes, an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible, should be considered as part of an overall CCS.	111. Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.
8.~~79~~83 The selection of components for the filtration system~~(including air, gas and vent filters)~~ and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the ~~products,~~ product, justified and documented ~~and justified~~. The filtration system should ~~not generate~~ minimize the generation of fibres and particulates, not cause or contribute to unacceptable levels of impurities ~~or~~, or possess characteristics that otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should be compatible with the fluid and not be adversely affected by the	8.81 The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the product, justified and documented. The filtration system should minimize the generation of fibres and particles, not cause or contribute to unacceptable levels of impurities, or possess characteristics that otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should be compatible with the fluid and not be adversely	112. Fibre-shedding characteristics of filters should be minimal. 115. The filter should not affect the product by removal of ingredients from it or by release of substances into it.

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product to be filtered. Adsorption of product components and extraction/leaching of filter components should be evaluated (~~see Single-Use Systems, Clauses 8.117-8.119).~~ refer to paragraph 8.125).	affected by the product to be filtered. Adsorption of product components and extraction/leaching of filter components should be evaluated (see paragraph 8.135).	
8.~~80~~84 The filtration system should be designed to: ~~a)~~ i. Allow operation within validated process parameters. ~~b)~~ ii. Maintain the sterility of the filtrate. ~~c)~~ iii. Minimize the number of aseptic connections required between the sterilizing filter and the final filling of the product. ~~d)~~ iv. Allow cleaning procedures to be conducted as necessary. ~~e)~~ v. Allow sterilization procedures, including ~~SIP~~ sterilization in place, to be conducted as necessary. ~~The sterilization procedures should be validated to ensure achievement of a target sterilization assurance level (SAL) of 10-6 or better (e.g. 10-7).~~ ~~f)~~ vi. Permit in-place integrity testing, of the 0.22 µm sterilizing filter, 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.	8.82 The filtration system should be designed to: i. Allow operation within validated process parameters. ii. Maintain the sterility of the filtrate. iii. Minimize the number of aseptic connections required between the final sterilising grade filter and the final filling of the product. iv. Allow cleaning procedures to be conducted as necessary. v. Allow sterilisation procedures, including sterilisation in place, to be conducted as necessary. vi. Permit in-place integrity testing, of the 0.22 µm final sterilising grade filter, preferably as a closed system, both prior to, and following filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.	N/A
8.~~81~~85 ~~Liquid sterilizing~~ Sterile filtration of liquids should be validated ~~during initial process validation.~~ in accordance with European (or other relevant) Pharmacopeia requirements.	8.83 Sterile filtration of liquids should be validated in accordance with relevant Pharmacopeia requirements. Validation can be grouped by different	N/A

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Validation can be grouped by different strengths or variations of a product~~,~~ but should be done under worst ~~-~~case conditions. The ~~rational~~ rationale for grouping ~~fluids~~ should be justified and documented.	strengths or variations of a product but should be done under worst-case conditions. The rationale for grouping should be justified and documented.	
8.~~82~~86 During filter validation, wherever possible, the product to be filtered should be used for bacterial retention testing of the sterilizing filter. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.	8.84 During filter validation, wherever possible, the product to be filtered should be used for bacterial retention testing of the sterilising grade filter. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.	N/A
8.~~83~~87 Filtration parameters that should be considered and established in validation and monitored in routine processing should include, but are not limited to: ~~a) If the system is flushed or integrity tested in-situ with a fluid other than the product, then flushing with the product should be part of the process.~~ ~~b)~~ i. The wetting fluid used for filter integrity testing should be based on the filter manufacturer's recommendation or the fluid to be filtered. ~~For the latter,~~ The appropriate integrity test value specification should be established. ~~c)~~ ii. If the system is flushed or integrity tested in-situ with a fluid other than the product, appropriate actions are taken to avoid any deleterious effect on product quality. iii. Filtration process conditions including: ~~i.~~ • Fluid ~~prefiltration~~ pre-filtration holding time and effect on bioburden. ~~ii.~~ • Filter conditioning, with fluid if necessary. ~~iii.~~ • Maximum filtration time/total time filter is in contact with fluid.	8.85 Filtration parameters that should be considered and established during validation should include, but are not limited to: i. The wetting fluid used for filter integrity testing: • It should be based on the filter manufacturer's recommendation or the fluid to be filtered. The appropriate integrity test value specification should be established. • If the system is flushed or integrity tested in-situ with a fluid other than the product, appropriate actions are taken to avoid any deleterious effect on product quality. ii. Filtration process conditions including: • Fluid pre-filtration holding time and effect on bioburden.	N/A

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~~iv~~ •Maximum operating pressure. •Flow rate. ~~v~~ •Maximum filtration volume. ~~vi.~~ •Temperature. ~~vii.~~ • The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter. ~~Any significant differences from those validated to those observed during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record.~~ 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.	• Filter conditioning, with fluid if necessary. • Maximum filtration time/total time filter is in contact with the fluid. • Maximum operating pressure. • Flow rate. • Maximum filtration volume. • Temperature. • The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.	
	8.86 Routine process controls should be implemented to ensure adherence to validated filtration parameters. Results of critical process parameters should be included in the batch record, including but not limited to the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter. Any significant difference from critical parameters during manufacturing should be documented and investigated.	N/A
8.~~84~~88 The integrity of the sterilized filter assembly should be verified by integrity testing before use, ~~in case of~~ to check for damage and loss of integrity caused by ~~processing, and~~ the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be ~~verified by on-line testing immediately after use by an appropriate method such as a~~	8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise a fluid should be subject to a	113. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk

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subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. Test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is ~~recognised~~ recognized that ~~for small batch sizes, this~~ pre-use post sterilization integrity testing (PUPSIT) may not always be possible~~;~~ after sterilization due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken ~~as long as~~ providing that a ~~formal~~ thorough risk assessment has been performed and compliance is achieved~~. There should be written integrity test methods~~ by the implementation of appropriate controls to mitigate any risk of non-sterility. Points to consider in such a risk assessment should include but are not be limited to: i. In depth knowledge and control of the sterilization process to ensure that the potential for damage to the filter is minimized. ii. In depth knowledge and control of the supply chain to include: •Contract sterilization facilities. •Defined transport mechanisms. •Packaging of the sterilized filter, to prevent damage to the filter during transportation and storage. iii. In depth process knowledge such as: •The specific product type, including ~~acceptance criteria, and failure investigation procedures and justified conditions under~~ particulate burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of	non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to: i. In depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized. ii. In depth knowledge and control of the supply chain to include: • Contract sterilisation facilities. • Defined transport mechanisms. • Packaging of the sterilised filter, to prevent damage to the filter during transportation and storage. iii. In depth process knowledge such as:	solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.

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a non-integral filter during a post-use filter integrity test. •Pre-filtration and processing steps, prior to the sterilizing filter, which ~~the filter integrity test can be repeated. Results of the integrity tests (including failed and repeated tests) should be included in the batch record.~~ would remove particulate burden and clarify the product prior to the sterile filtration.	• The specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test. • Pre-filtration and processing steps, prior to the final sterilising grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.	
8.~~85~~89 The integrity of critical sterile gas and air vent filters ~~in the filter assembly~~ (that are directly linked to the sterility of the product) should be verified by testing after use~~.~~, with the filter remaining in the filter assembly.	8.88 The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly or housing.	N/A
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 post-use. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses and sterilization cycles permitted).	8.89 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, integrity testing should be carried out at installation and prior to replacement. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses and heat treatment/sterilisation cycles permitted as applicable).	N/A
8.~~86~~91 For gas filtration, ~~the avoidance of~~ attention should be paid to avoiding unintended moistening or wetting of the filter or filter equipment ~~is important~~. This can be achieved by the use of hydrophobic filters.	8.90 For gas filtration, unintended moistening or wetting of the filter or filter equipment should be avoided.	N/A
8.~~87~~92 ~~Where serial~~ If the sterilizing filtration ~~(one filtration is~~	8.91 If the sterilising filtration process has been	N/A

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~~followed by a subsequent filtration) is a~~ process ~~requirement the filter train~~has been validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilizing unit and all ~~sterilizing grade~~ filters within ~~it~~the system should satisfactorily pass integrity testing ~~both before use, in case of damage during processing, and~~ after use.	validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilising unit and all filters within the system should satisfactorily pass integrity testing after use.	
8.~~88~~93 ~~Where~~ In a redundant filtration system (where a second filter is present as a backup but the sterilizing process is validated as only requiring one filter ~~is used, the additional filter does not require~~), post-use integrity ~~testing unless~~ test of the primary sterilizing filter ~~fails, in which case the redundant filter must~~ should be performed and if demonstrated to be integral, then ~~satisfactorily pass~~ a post-use integrity ~~testing.~~ test of the secondary filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, a risk assessment should be carried out to determine the acceptability of performing a post-use integrity test on the secondary (redundant) filter.	8.92 In a redundant filtration system (where a second redundant sterilising grade filter is present as a backup but the sterilising process is validated as only requiring one filter), post-use integrity test of the primary sterilising grade filter should be performed and if demonstrated to be integral, then a post-use integrity test of the redundant (backup) filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, post-use integrity test on the secondary (redundant) filter should be performed, in conjunction with an investigation and risk assessment to determine the reason for the primary filter test failure.	N/A
8.94 Bioburden samples should be taken from the bulk product and immediately prior to the ~~first filter and the sterilizing filter,~~ final sterile filtration. Systems for taking samples should be designed so as not to introduce contamination.	8.93 Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. In case where a redundant filtration set-up is used, it should be taken prior to the first filter. Systems for taking samples should be designed so as not to introduce contamination.	N/A
8.~~89~~95 Liquid sterilizing filters should be discarded after the processing of a single lot~~.~~ and the same filter should not be used for more than one working day unless such use has been validated.	8.94 Liquid sterilising grade filters should be discarded after the processing of a single batch and the same filter should not be used continuously for more than one working day unless such use has been validated.	114. The same filter should not be used for more than one working day unless such use has been validated.

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8.96 Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should: i. Assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid. ii. Conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the sterilizing filter or filtrate quality. iii. Document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained. iv. Implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use.	8.95 Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should: i. Assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid. ii. Conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the final sterilising grade filter or filtrate quality. iii. Document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained. iv. Implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use.	N/A
Form-Fill-Seal	Form-Fill-Seal (FFS)	N/A
N/A	8.96 The conditions for FFS machines used for terminally sterilised products should comply with the environmental requirements of paragraphs 8.3 and 8.4 of this Annex. The conditions for FFS machines used in aseptic manufacture should comply with the environmental requirements of paragraph 8.10 of this	N/A

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N/A	8.97 Contamination of the packaging films used in the FFS process should be minimized by appropriate controls during component fabrication, supply and handling. Due to the criticality of packaging films, procedures should be implemented to ensure that the films supplied meet defined specifications and are of the appropriate quality, including material thickness and strength, microbial and particulate contamination, integrity and artwork, as relevant. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of packaging films and associated components should be defined and controlled within the PQS and considered in the CCS.	N/A
~~8.90~~ 8.97 Form-Fill-Seal (FFS) units include blow moulding from thermoplastic granulate and thermoforming from thermoplastic film, typically known as Blow-Fill-Seal (BFS) and Vertical-Form- Fill-Seal (VFFS), respectively. VFFS process is an automated filling process, typically for terminally sterilized products, that may utilize a single or dual web system which constructs the primary container out of a flat roll of thermoplastic film while simultaneously filling the formed bags with product and sealing the filled bags in a continuous process. All such containers are considered to be ~~sealed~~ closed through sealing by fusion and, as such, fall under the requirement to perform 100% integrity testing (refer to paragraph 8.21).		N/A
~~8.91~~ 8.98 Process parameters relating to seal integrity should be ~~validated~~ qualified and appropriately controlled. ~~Critical parameters include, but are not limited to: seal strength, seal~~	8.98 Particular attention should be given to understanding and assessing the operation of the equipment, including set-up, filling, sealing and	N/A

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~~uniformity, sealing temperatures, pressures, sealing times and dwell time for filling. Seal strength and uniformity should be monitored routinely.~~	cutting processes, so that critical process parameters are understood, validated, controlled and monitored appropriately.	
N/A	8.99 Any product contact gases, e.g. those used to inflate the container or used as a product overlay, should be appropriately filtered, as close to the point of use as possible. The quality of gases used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.	N/A
~~8.92 Samples of filled containers should be tested for general performance e.g. ease-of-opening, and Seal uniformity. Sample size and frequency should be based on the principles of QRM.~~	N/A	N/A
8.99	转至 8.101	N/A
8.100 Seal strength and uniformity should be monitored routinely.	N/A	N/A
~~8.94~~ 8.101 ~~Risk management principles should be used to justify the machine's design and operational controls. These~~ The controls identified during qualification should be in alignment with the site's ~~contamination control strategy~~ CCS. Aspects to be considered include ~~(~~but are not limited to~~)~~: ~~a)~~ i. Determination of the boundaries of the critical zone ~~that should be protected from contamination, and its control~~. ~~b)~~ ii. Environmental control and monitoring, both of the ~~BFS~~ machine and the background in which it is placed. ~~c)~~ iii. Integrity testing of the ~~BFS~~ product ~~pathways~~ filling lines. iv. Integrity testing of the cooling system. ~~d)~~ v. Duration of the batch or filling campaign. ~~e)~~ vi. Control of polymer starting material (including resin	8.100 The controls identified during qualification of FFS should be in alignment with the CCS. Aspects to be considered include but are not limited to: i. Determination of the boundaries of the critical zone. ii. Environmental control and monitoring, both of the machine and the background in which it is placed. iii. Personnel gowning requirements. iv. Integrity testing of the product filling lines and	27. Because of this special technology particular attention should be paid to, at least the following: • equipment design and qualification • validation and reproducibility of cleaning-in-place and sterilisation-in-place • background clean room environment in which the equipment is located • operator training and clothing • interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

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pellets). ~~f)~~ vii. Cleaning-in-place and sterilization-in-place of equipment in direct contact to the formulation (product filling lines); ~~and air and product pathways~~ sterilization-in-place of sterile air pathways.	filtration systems (as relevant). v. Duration of the batch or filling campaign. vi. Control of packaging films, including any requirements for film decontamination or sterilisation. vii. Cleaning-in-place and sterilisation-in-place of equipment as necessary. viii. Machine operation, settings and alarm management (as relevant).	
8.99 Critical parameters include, but are not limited to: i. Seal strength. ii. Seal uniformity. iii. Sealing temperatures. iv. Sealing pressures. v. Sealing times. vi. Dwell time for filling.	8.101 Critical process parameters for FFS should be determined during equipment qualification and should include, but are not limited to: i. Settings for uniform package dimensions and cutting in accordance with validated parameters. ii. Setting, maintenance and monitoring of validated forming temperatures (including pre-heating and cooling), forming times and pressures as relevant. iii. Setting, maintenance and monitoring of validated sealing temperatures, sealing temperature uniformity across the seal, sealing times and pressures as relevant. iv. Environmental and product temperature.	N/A

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	v. Batch-specific testing of package seal strength and uniformity. vi. Settings for correct filling volumes, speeds and uniformity. vii. Settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity is not compromised. viii. Methods and parameters for integrity testing of filled containers (see paragraph 8.22).	
N/A	8.102 Appropriate procedures for the verification, monitoring and recording of FFS critical process parameters and equipment operation should be applied during production.	N/A
N/A	8.103 Operational procedures should describe how forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.	N/A
N/A	8.104 Appropriate maintenance procedures should be established based on risk, and include maintenance and inspection plans for tooling critical to the effectiveness of unit sealing. Any issues identified that indicate a potential product quality concern should be documented and investigated.	N/A
Blow-Fill-Seal ~~technology~~	Blow-Fill-Seal	Blow/fill/seal technology
~~8.93~~ 8.102	转至 8.110	N/A
~~8.100~~ 8.106 Blow-Fill-Seal equipment used for ~~production~~ the manufacture of products which are terminally sterilized should	8.105 Blow-Fill-Seal equipment used for the manufacture of products which are terminally	26. Blow/fill/seal units are purpose built machines in which, in one continuous

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be installed in at least a Grade D environment. The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 and 8.4.	sterilised should be installed in at least a grade D environment. The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 and 8.4.	operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilised should be installed in at least a grade D environment.
~~8.94~~ 8.101	转至 8.100	27
~~8.95 Shuttle and Rotary type equipment used for aseptic production which is fitted with an effective grade A air shower should be installed in at least a grade C environment, provided that grade A/B clothing is used.~~	8.106 BFS used for aseptic processing: i. For shuttle type equipment used for aseptic filling, the parison is open to the environment and therefore the areas where parison extrusion, blow-moulding and sealing take place should meet grade A conditions at the critical zones. The filling environment should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation. ii. For rotary-type equipment used for aseptic filling, the parison is generally closed to the environment once formed, the filling environment within the parison should be	26. Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilised should be installed in at least a grade D environment.
~~8.96~~ 8.103 For Shuttle type equipment, ~~the environment should comply with the viable and non-viable limits at rest and the viable limit only when in operation. The shuttle zone should meet grade A viable limits.~~ used for aseptic filling, the area between parison cutting and mould sealing should be covered by a flow of filtered air to provide Grade A conditions at the critical zone. The equipment should be installed in at least a Grade C environment, provided that Grade A/B clothing is used. The filling environment should meet Grade A for viable and non-viable limits at rest and the viable limit only when in operation.		
~~8.97~~ 8.104 For rotary-type equipment ~~the environment should~~		

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~~comply with the viable and non-viable limits "at rest"~~, used for aseptic filling, the filling environment should be designed to meet Grade A conditions. ~~It is not normally possible to perform environmental monitoring with the parison during operation.~~ Other sterility assurance controls such as monitoring of ~~the background environment~~ critical parameters and alarms during each batch and parison support filter integrity testing should be ~~performed in accordance with risk management principles~~ considered.	designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation. iii. The equipment should be installed in at least a grade C environment, provided that grade A/B clothing is used. The microbiological monitoring of operators wearing grade A/B clothing in a grade C area, should be performed in accordance with risk management principles, and the limits and monitoring frequencies applied with consideration of the activities performed by these operators.	
N/A	8.107 Due to the generation of particles from polymer extrusion and cutting during operation, and the restrictive size of critical filling zones of BFS equipment, in operation monitoring of total particle for BFS equipment is not expected. However, data should be available to demonstrate that the design of the equipment ensures that critical zones of the filling process environment would meet grade A conditions in operation.	N/A
N/A	8.108 Viable environmental monitoring of BFS processes should be risk-based, and designed in accordance with section 9 of this Annex. In operation viable monitoring should be undertaken for the full duration of critical processing, including equipment assembly. For rotary-type BFS equipment, it is acknowledged that monitoring of the critical filling zone may not be possible.	N/A
~~8.98~~ 8.105 The environmental control and monitoring program	8.109 The environmental control and monitoring	N/A

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should take into consideration the moving parts and complex ~~gas~~ airflow paths generated by the BFS process and the effect of the high heat outputs of the process, e.g. by performing smoke studies and/or other equivalent studies. Environmental monitoring should be applied taking into consideration elements such as air-filter configuration, air filter integrity, cooling systems integrity, equipment design and installation.	programme should take into consideration the moving parts and complex airflow paths generated by the BFS process and the effect of the high heat outputs of the process, (e.g. through the use of airflow visualization studies and/or other equivalent studies). Environmental monitoring programmes should also consider factors such as air-filter configuration, air-filter integrity, cooling systems integrity (see paragraph 6.21), equipment design and qualification.	
~~8.100~~ 8.106	转至 8.105	26.
~~8.93~~ 8.102 Blow-Fill-Seal (BFS) units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed~~, all~~ by ~~the~~ one automatic machine~~, see glossary for full definition~~. Air that makes contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container should undergo appropriate filtration.	8.110 Air or other gases that make contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container should undergo appropriate filtration. The quality of gas used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.	N/A
~~8.101~~ 8.107 External ~~particle~~ particulate and microbial contamination of the polymer should be prevented by appropriate design, control, and maintenance of the polymer storage, sampling and distribution systems. The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be fully understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxins levels of the raw polymer should be defined and controlled within the CCS.	8.111 Particulate and microbial contamination of the polymer granulate should be prevented by appropriate design, control, and maintenance of the polymer granulate storage, sampling and distribution systems.	N/A
	8.112 The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of the raw polymer should be defined and controlled within the PQS and considered in the CCS.	N/A
~~8.102~~ 8.108 Interventions requiring cessation of filling and/or	8.113 Interventions requiring cessation of filling	N/A

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~~blowing~~ extrusion, moulding and sealing and, where required, re-sterilization of the filling machine should be clearly defined and well described in the aseptic filling procedure, and included in the ~~aseptic process simulation~~ APS (refer ~~clause~~ to paragraphs 9.36, 9.37 and 9.38).	and/or extrusion, moulding and sealing and, where required, re-sterilisation of the filling machine should be clearly defined and described in the filling procedure, and included in the APS as relevant (see paragraphs 9.34, 9.35 and 9.36).	
N/A	8.114 The controls identified during qualification of BFS should be in alignment with the site's CCS. Aspects to be considered include but are not limited to: i. Determination of the boundaries of the critical zone. ii. Environmental control and monitoring, both of the machine and the background in which it is placed. iii. Personnel gowning requirements. iv. Integrity testing of the product filling lines and filtration systems (as relevant). v. Duration of the batch or filling campaign. vi. Control of polymer granulate, including distribution systems and critical extrusion temperatures. vii. Cleaning-in-place and sterilisation-in-place of equipment as necessary.	N/A

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	viii. Machine operation, settings and alarm management (as relevant).	
N/A	8.115 Critical process parameters for BFS should be determined during equipment qualification and should include, but are not limited to: i. Clean-in-place and sterilisation-in-place of product pipelines and filling needles (mandrels). ii. Setting, maintenance and monitoring of extrusion parameters, including temperature, speed and extruder throat settings for parison thickness. iii. Setting, maintenance and monitoring of mould temperatures, including rate of cooling where necessary for product stability. iv. Preparation and sterilisation of ancillary components added to the moulded unit, e.g. bottle caps. v. Environmental control, cleaning, sterilisation and monitoring of the critical extrusion, transfer and filling areas as relevant. vi. Batch-specific testing of package wall-thickness at critical points of the container. vii. Settings for correct filling volumes, speeds	N/A

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	and uniformity. viii. Settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity and quality is not compromised. ix. Methods and parameters for integrity testing of 100% of all filled containers (see paragraph 8.22). x. Settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).	
N/A	8.116 Appropriate procedures for the verification, monitoring and recording of BFS critical process parameters and equipment operation should be applied during production.	N/A
N/A	8.117 Operational procedures should describe how blowing, forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.	N/A
~~8.103 Process validation should take into consideration critical operating parameters and variables of the equipment that impact on the quality of the product, e.g. filling speed, extrusion temperature, filling times.~~	N/A	N/A
~~8.104 Samples of filled containers should be tested for general performance e.g. ease of opening and wall thickness; sample size and frequency should be based on the principles of QRM.~~	N/A	N/A
N/A	8.118 Where the BFS process includes the addition of components to moulded containers (e.g. addition of caps to LVP bottles), these components should be	N/A

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	appropriately decontaminated and added to the process using a clean, controlled process. i. For aseptic processes, the addition of components should be performed under grade A conditions, to ensure the sterility of critical surfaces, using pre-sterilised components. ii. For terminally sterilised products, the validation of terminal sterilisation processes should ensure the sterility of all critical product pathways between the component and moulded container, including areas that are not wetted during sterilisation. iii. Testing procedures should be established and validated to ensure the effective sealing of components and moulded containers.	
N/A	8.119 Appropriate maintenance procedures should be established based on risk, and include maintenance and inspection plans for items critical to unit sealing, integrity and sterility.	N/A
8.109 The moulds used to form containers are considered critical equipment and any changes or modification to moulds should result in an assessment of finished product container integrity, and should be supported by validation.	8.120 The moulds used to form containers are considered critical equipment and any changes or modification to moulds should result in an assessment of finished product container integrity, and where the assessment indicates, should be supported by validation. Any issues identified that indicate a potential product quality concern should be documented and investigated.	N/A
Lyophilization	Lyophilization	N/A

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~~8.105~~ 8.110 Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of ~~that~~ the sterilized product ~~or material~~. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particulate contamination between the filling ~~operation~~ of products for lyophilization, and completion of lyophilization process. All control measures in place should be determined by the site's ~~contamination control strategy~~ CCS.	8.121 Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of the sterilised product. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particle contamination between the filling of products for lyophilization, and completion of lyophilization process. All control measures in place should be determined by the site's CCS.	N/A
~~8.106~~ 8.111 The sterilization of lyophilizers and associated equipment, (e.g. trays, vial support rings) should be validated and holding times between sterilization cycles appropriately challenged during aseptic process simulations. The lyophilizer should be sterilized ~~before each load~~ regularly, based on system design. Re-sterilization should be performed following maintenance or cleaning. ~~The~~ Sterilized lyophilizers and associated equipment should be protected from contamination after sterilization.	8.122 The sterilisation of the lyophilizer and associated equipment (e.g. trays, vial support rings) should be validated and the holding time between the sterilisation cycle and use appropriately challenged during APS (see paragraph 9.33). The lyophilizer should be sterilised regularly, based on system design. Re-sterilisation should be performed following maintenance or cleaning. Sterilised lyophilizers and associated equipment should be protected from contamination after sterilisation.	N/A
~~8.107 Where there is a closing system for partially closed containers, the surfaces of any equipment protruding into the chamber to effect sealing should also be sterilized.~~	N/A	N/A
8.112 Lyophilizers that are manually loaded or unloaded should normally be sterilized before each load. For lyophilizers loaded by automated closed systems or located within systems that exclude operator intervention, the frequency of sterilization should be justified and documented as part of the CCS.	8.123 Lyophilizers and associated product transfer and loading/unloading areas should be designed to minimize operator intervention as far as possible. The frequency of lyophilizer sterilisation should be determined based on the design and risks related to system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier	N/A

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	technology separation should be sterilised before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilisation should be justified and documented as part of the CCS.	
~~8.109~~ 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 certification. The frequency of vacuum/leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.	8.124 The integrity of the lyophilizer should be maintained following sterilisation and during lyophilization. The filter used to maintain lyophilizer integrity should be sterilised before each use of the system and its integrity testing results should be part of the batch certification/release. 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.	N/A
~~8.108~~ 8.114 Lyophilization trays should be checked ~~regularly~~ to ensure that they are not misshapen ~~and~~ or damaged.	8.125 Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.	N/A
~~8.110 The integrity of the system should be monitored periodically along with consideration of the leak rate test.~~	N/A	N/A
~~8.111~~ 8.115 ~~with regard to~~ Points to consider for the design of loading (and unloading ~~the lyophilizer~~, where the lyophilised material is not in a sealed container (e.g. open tray dried materials), include but are not limited to: ~~a)~~ i. The loading pattern within the lyophilizer should be specified and documented. ~~b)~~ ii. ~~Transport~~ The transfer of partially closed containers to ~~the~~ a lyophilizer ~~and loading of filled product, or other equipment into the lyophilizer~~ should ~~take place~~ be undertaken under ~~a~~ Grade A ~~environment~~ conditions at all times and handled in a manner designed to minimize direct	8.126 Points to consider for the design of loading (and unloading, where the lyophilised material is still unsealed and exposed), include but are not limited to: i. The loading pattern within the lyophilizer should be specified and documented. ii. The transfer of partially closed containers to a lyophilizer should be undertaken under grade A conditions at all times and handled in a manner designed to minimize direct operator	N/A

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operator intervention. Technologies such as conveyor systems, portable transfer systems (e.g. clean air transfer carts, portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained). Alternatively, where supported by validation, containers closed in the Grade A zone and not reopened whilst in the Grade B may be used to protect partially stoppered vials (e.g. sealed sterilized trays). ~~c)~~ iii. Airflow patterns should not be adversely affected by transport devices and venting of the loading zone. iv. Unsealed containers (such as partially stoppered vials) should be maintained under Grade A ~~environment~~ conditions and should normally be separated from operators by physical barrier technology or any other appropriate measures. ~~d)~~ v. Where seating of the stoppers is not completed prior to opening the lyophilizer chamber, product removed from the lyophilizer should remain under ~~a~~ Grade A ~~environment~~ conditions during subsequent handling. ~~e)~~ vi. Utensils used during transfer to~~,~~ and loading and unloading of~~,~~ the lyophilizer (such as trays, bags, placing devices, tweezers, etc.) should be subject to a validated sterilization process.	intervention. Technologies such as conveyor systems or portable transfer systems (e.g. clean air transfer carts, portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained. Alternatively, where supported by validation, trays closed in grade A and not reopened whilst in the grade B area may be used to protect partially stoppered vials (e.g. appropriately closed boxes). iii. Airflow patterns should not be adversely affected by transport devices and venting of the loading zone. iv. Unsealed containers (such as partially stoppered vials) should be maintained under grade A conditions and should normally be separated from operators by physical barrier technology or any other appropriate measures. v. Where seating of the stoppers is not completed prior to opening the lyophilizer chamber, product removed from the lyophilizer should remain under grade A conditions during subsequent handling. vi. Utensils used during loading and unloading of the lyophilizer (e.g. trays, bags, placing devices, tweezers) should be sterile.	

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Closed systems	Closed systems	N/A
~~8.112~~ 8.116 Closed systems can be ~~both~~ single use systems ~~(SUS)~~ (i.e. disposable systems) and fixed systems (such as vessels with fixed pipework). Guidance in this section is equally applicable to both systems.		N/A
~~8.113~~ 8.117 The use of closed systems can reduce the risk of ~~both~~ extraneous contamination such as microbial, particulate and chemical ~~contamination due to interventions~~ from the adjacent environment. Closed systems should always be designed to reduce the need for, and complexity of manual interventions.	8.127 The use of closed systems can reduce the risk of microbial, particle and chemical contamination from the adjacent environment. Closed systems should always be designed to reduce the need for manual manipulations and the associated risks.	N/A
~~8.114~~ 8.118 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing ~~must~~ should ensure maintenance of sterility. ~~Tubing/pipework that is not assembled prior to sterilization~~ Connection of sterile equipment (e.g. tubing / pipework) to the sterilized product pathway after the final sterilizing filter should be designed to be connected aseptically (e.g. by intrinsic aseptic connectors or fusion systems).	8.128 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing/pipework) to the sterilised product pathway after the final sterilising grade filter should be designed to be connected aseptically (e.g. by intrinsic sterile connection devices).	N/A
~~8.115~~ 8.119 Appropriate measures should be in place to ensure the integrity of ~~those~~ components used in aseptic connections. The ~~manner in~~ means by which this is ~~conducted~~ achieved should be determined ~~based on QRM principles~~ and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.	8.129 Appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.	N/A
~~8.116~~ 8.120 The background in which closed systems are located ~~will vary~~ should be based on their design and the	8.130 The background environment in which closed systems are located should be based on their design	N/A

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processes undertaken. ~~If there is a high risk that the system will not remain integral during processing, it~~ For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in a Grade A ~~environment~~ zone. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower ~~grade, including grade D, can~~ classified area may be ~~considered~~ used. If the closed system is opened (e.g. for maintenance of a bulk manufacturing line) then this should be performed in a classified area appropriate to the materials (e.g. Grade C for terminally sterilization processes, or Grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilization in case of aseptic processes).	and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in grade A. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may be used. Any transfer between classified areas should be thoroughly assessed (see paragraph 4.10). If the closed system is opened (e.g. for maintenance of a bulk manufacturing line) then this should be performed in a classified area appropriate to the materials (e.g. grade C for terminal sterilisation processes, or grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilisation in case of aseptic processes).	
Single use systems (SUS)	Single use systems (SUS)	N/A
~~8.117~~ 8.121 ~~Single use systems (~~SUS~~)~~ are those technologies used in manufacture of sterile ~~medicinal~~ products which are ~~designed~~ used as an alternative to ~~replace~~ reusable equipment. SUS ~~are typically defined systems~~ can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors.	8.131 SUS are those technologies used in manufacture of sterile products which are used as an alternative to reusable equipment. SUS can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors. Single use systems should be designed to reduce the need for manipulations and complexity of manual interventions.	N/A
~~8.118~~ 8.122 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to: ~~a)~~ i. The interaction between the product and product contact surface (such as adsorption, or the formation of leachables and extractables).	8.132 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to: i. The interaction between the product and product contact surface (such as adsorption, or	N/A

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~~b)~~ ii. ~~More fragile than~~ The fragile nature of the system compared to fixed reusable systems. ~~c)~~ iii. The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made. ~~d)~~ iv. ~~Design~~ The complexity of the assembly. ~~e)~~ v. The performance of the pre-use integrity test for sterilizing grade filters (refer to ~~clause 8.84~~ paragraph 8.88). ~~f) Integrity testing.~~ ~~g)~~ vi. ~~Pin hole~~ The risk of holes and leakage. ~~h)~~ vii. The potential for compromising the system at the point of opening the outer packaging. ~~i) Assessment of suppliers of disposable systems (including sterilization of these disposable systems).~~ ~~j)~~ viii. The risk of particulate contamination.	leachables and extractables). ii. The fragile nature of the system compared with fixed reusable systems. iii. The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made. iv. The complexity of the assembly. v. The performance of the pre- and post-use integrity testing for sterilising grade filters (see paragraph 8.87). vi. The risk of holes and leakage. vii. The potential for compromising the system at the point of opening the outer packaging. viii. The risk of particle contamination.	
8.123 Sterilization processes for SUS should be validated and shown to have no adverse impact on system performance.	8.133 Sterilisation processes for SUS should be validated and shown to have no adverse impact on system performance.	N/A
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.	8.134 Assessment of suppliers of disposable systems including sterilisation is critical to the selection and use of these systems. For sterile SUS, verification of sterility assurance should be performed as part of the supplier qualification and evidence of sterilisation of each unit should be checked on receipt.	N/A

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~~8.119~~ 8.125 ~~The compatibility of materials used for~~ The adsorption and reactivity of the product with product contact surfaces ~~with the products~~ should be ~~ensured~~ evaluated under ~~the~~ process conditions ~~by evaluating e.g. adsorption and reactivity to the product~~.	8.135 The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions.	N/A
~~8.120~~ 8.126 ~~Extractable profile data obtained from the supplier of the components of SUS may be useful to ensure that extractables and leachables from the SUS do not alter the quality of the product.~~ The extractable and leachable profile of the SUS and any impact on the quality of the product especially where the system is made from polymer-based materials should be evaluated. An ~~risk~~ assessment should be ~~conducted~~ carried out for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk ~~to~~ from leachables, including those ~~taking up leachables extensively or stored for longer periods,~~ that may absorb processed materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, should be taken into consideration~~, as necessary~~. If applying simulated processing conditions, these should accurately reflect the actual processing conditions and be based on a scientific rationale.	8.136 The extractable and leachable profiles of the SUS and any impact on the quality of the product especially where the system is made from polymer-based materials should be evaluated. An assessment should be carried out for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk from leachables, including those that may absorb processed materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, should be taken into consideration. If applying simulated processing conditions, these should accurately reflect the actual processing conditions and be based on a scientific rationale.	N/A
~~8.121~~ 8.127 SUS should be designed ~~so as~~ to maintain integrity ~~during~~ throughout processing under the intended operational conditions ~~and duration, especiall~~. Attention to the structural integrity of the single use components ~~under~~ is necessary where these may be exposed to more extreme ~~process and transport~~ conditions ~~such as~~ (e.g. freezing and thawing processes) either during routine processing or transportation. This should include verification that intrinsic aseptic connections (both heat sealed and mechanically	8.137 SUS should be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single use components is necessary where these may be exposed to more extreme conditions (e.g. freezing and thawing processes) either during routine processing or transportation. This should include verification that intrinsic sterile connection devices (both heat sealed and	N/A

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sealed) remain integral under these conditions.	mechanically sealed) remain integral under these conditions.	
~~8.122~~ 8.128 Acceptance ~~procedures~~ criteria should be established and implemented for SUS corresponding to the risks or criticality of the products and its processes. On receipt, each piece of SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. ~~a~~ A visual inspection of the outer packaging (e.g. appearance of exterior carton, product pouches), label printing, and review of attached documents (e.g. certificate of ~~Analysis, radiation certificate~~ conformance and proof of sterilization) should be carried out and documented prior to use. ~~Prior to use, each piece of SUS should be checked to ensure that they have been manufactured and delivered in accordance with the approved specification.~~	8.138 Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the products and its processes. On receipt, each piece of SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (e.g. appearance of exterior carton, product pouches), label printing, and review of attached documents (e.g. certificate of conformance and proof of sterilisation) should be carried out and documented prior to use.	N/A
~~8.123~~ 8.129 Critical manual handling operations of SUS such as assembly~~ing~~ and ~~connecting~~ connections should be subject to appropriate controls and verified during the ~~aseptic process simulation test~~ APS.	8.139 Critical manual handling operations of SUS such as assembly and connections should be subject to appropriate controls and verified during APS.	N/A

9 Environmental and process monitoring

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General	General	N/A
9.1 The site's environmental and process monitoring program forms part of the overall contamination control strategy and is used to monitor the controls designed to minimize the risk of microbial and particulate contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, their reliability is dependent on the design, validation and operation of the system that they are monitoring.	9.1 The site's environmental and process monitoring programme forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particle contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, the results help confirm the reliability of the design, validation and operation of the system that they are monitoring.	N/A
9.2 This program is typically comprised of the following elements: a) Environmental monitoring – non viable particles. b) Environmental and personnel monitoring – viable particles. c) Aseptic process simulation (aseptically manufactured product only).	9.2 This programme is typically comprised of the following elements: i. Environmental monitoring – total particle. ii. Environmental and personnel monitoring – viable particle. iii. Temperature, relative humidity and other specific characteristics. iv. APS (aseptically manufactured product only).	N/A
9.3 ~~These key elements provide information with regards to the process and facility capabilities with respect to the maintenance of sterility assurance.~~ The information from these systems should be used for routine batch release and for periodic assessment during process review or investigations. This applies for both terminal sterilization	9.3 The information from these systems should be used for routine batch certification/release and for periodic assessment during process review or investigation. This applies for both terminal sterilisation and aseptic processes, however, the criticality of the impact may differ depending upon the product and process type.	N/A

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and aseptic processes, however, the criticality of the impact may differ depending upon the product and process type.		
Environmental monitoring	Environmental and process monitoring	Clean room and clean air device monitoring
9.4–Risk assessments should be performed in order to establish a comprehensive environmental monitoring program, ~~In order to establish a robust environmental monitoring program~~, i.e. sampling locations, frequency of monitoring， monitoring method used and incubation conditions (e.g. time, temperature(s) and aerobic and or anaerobic conditions), These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, specific processes, the operations involved, historical monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment. Consideration of other information such as air visualization studies should also be included. ~~appropriate risk assessments should be conducted based on detailed knowledge of the process inputs, the facility, equipment, specific processes, operations involved and knowledge of the typical microbial flora found, consideration of other aspects such as air visualization studies should also be included.~~ These risk assessments should be re-evaluated at defined intervals in order to confirm the effectiveness of the site's environmental monitoring program, the monitoring program ~~and they~~ should be considered in the overall context of the trend analysis and the contamination control strategy for the site.	9.4 An environmental monitoring programme should be established and documented. The purpose of the environmental monitoring programme, is to: i. Provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness, in accordance with design and regulatory requirements. ii. Effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality. Risk assessments should be performed in order to establish this comprehensive environmental monitoring programme, i.e. sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions). These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment.	N/A

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	The risk assessment should include the determination of critical monitoring locations, those locations where the presence of microorganisms during processing may have an impact upon product quality, (e.g. grade A, aseptic processing areas and the grade B areas that directly interface with the grade A area). Consideration of other information such as air visualisation studies should also be included. These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring programme. The monitoring programme should be considered in the overall context of the trend analysis and the CCS for the site.	
9.5 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.~~	9.5 Routine monitoring of cleanrooms, clean air equipment and personnel should be performed in operation throughout all critical stages of processing, including equipment set-up.	8. Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.
4.35	9.6 Other characteristics, such as temperature and relative humidity, should be controlled within ranges that align with product/processing/personnel requirements and support maintenance of defined cleanliness standards (e.g. grade A or B).	
9.6 The monitoring of Grade A zones should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should ~~also~~ be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, container, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be	9.7 The monitoring of grade A should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, containers, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and	N/A

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justified and appropriate to obtain reliable data from the critical zones. ~~outside of operations within the area, e.g. pre disinfection, post disinfection, prior to start of manufacturing and after a shutdown period etc., in order to detect potential incidents of contamination which may affect the controls within the areas. The number of samples and frequency of monitoring should be considered in the context of the risk assessments and contamination control strategy.~~	appropriate to obtain reliable data from the critical zones.	
9.7 Sampling methods should not pose a risk of contamination to the manufacturing operations. ~~For grade A monitoring, it is important that sampling should be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, container closures and product in order to evaluate maintenance of aseptic conditions during critical operations.~~	9.8 Sampling methods should not pose a risk of contamination to the manufacturing operations.	N/A
9.8 Appropriate alert and action limits should be set for the results of viable and non-viable particle monitoring ~~particulate and microbiological~~. Alert levels should be established based on results of cleanroom Performance Qualification (PQ) tests or trend data and should be subject to periodic review.	9.9 Appropriate alert levels and action limits should be set for the results of viable and total particle monitoring. The maximum total particle action limits are described in Table 5 and the maximum viable particle action limits are described in Table 6. However, more stringent action limits may be applied based on data trending, the nature of the process or as determined within the CCS. Both viable and total particle alert levels should be established based on results of cleanroom qualification tests and periodically reviewed based on ongoing trend data.	20. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.
9.9 Alert levels for Grade A (non-viable particles only) ~~The alert limits for~~ Grade B, Grade c and Grade D should be set such that adverse trends (e.g. a numbers of events or	9.10 Alert levels for grade A (total particle only) grade B, grade C and grade D should be set such that adverse trends (e.g. a numbers of events or individual events that indicate a	N/A

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individual events that indicate a deterioration of cleanliness) are detected and addressed. ~~based on the area performance, with the aim to have limits lower than those specified as action limits, in order to minimise risks associated and identify potential changes that may be detrimental to the process.~~	deterioration of environmental control) are detected and addressed.	
9.10 Monitoring procedures should define the approach to trending. Trends can include, but are not limited to: i. Increasing numbers of action limit or alert level breaches. ii. Consecutive breaches of alert levels. iii. Regular but isolated breaches of action limits that may have a common cause, for example single excursions that always follow planned preventative maintenance. iv. Changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to objectionable organisms or those that can be difficult to control such as spore-forming microorganisms.	9.11 Monitoring procedures should define the approach to trending. Trends should include, but are not limited to: i. Increasing numbers of excursions from action limits or alert levels. ii. Consecutive excursions from alert levels. iii. Regular but isolated excursion from action limits that may have a common cause, (e.g. single excursions that always follow planned preventative maintenance). iv. Changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds.	N/A
9.11 The monitoring of Grade C and D cleanrooms in operation should be performed based on data collected during qualification and historical data to allow effective trend analysis. The requirements of alert levels and action limits will depend on the nature of the operations carried out. Action limits may be more stringent than those listed in Table 6 and Table 7.	9.12 The monitoring of grade C and D cleanrooms in operation should be performed based on data collected during qualification and routine data to allow effective trend analysis. The requirements of alert levels and action limits will depend on the nature of the operations carried out. Action limits may be more stringent than those listed in Table 5 and Table 6.	N/A

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9.102 If action limits are exceeded, operating procedures should prescribe a root cause investigation, an assessment of the potential impact to product and requirements for ~~followed by~~ corrective and preventive actions. If alert ~~limits~~ levels are exceeded, operating procedures should prescribe ~~scrutiny~~ assessment and follow up, which ~~might~~ should include consideration of an investigation and/or corrective actions to avoid any further deterioration of the environment.	9.13 If action limits are exceeded, operating procedures should prescribe a root cause investigation, an assessment of the potential impact to product (including batches produced between the monitoring and reporting) and requirements for corrective and preventive actions. If alert levels are exceeded, operating procedures should prescribe assessment and follow-up, which should include consideration of an investigation and/or corrective actions to avoid any further deterioration of the environment.	N/A
9.113 ~~Surfaces and personnel should be monitored after critical operations.~~ Results from environmental monitoring should be considered when reviewing batch documentation for finished product batch certification ~~release~~.	N/A	N/A
Environmental monitoring- non-viable particles ~~Non-viable monitoring~~	Environmental monitoring – total particle	Clean room and clean air device monitoring
9.142 Non-viable particle monitoring systems should be established to obtain data for assessing potential contamination risks and to maintain the environment for sterile operations in the qualified state.	9.14 A total particle monitoring program should be established to obtain data for assessing potential contamination risks and to ensure the maintenance of the environment for sterile operations in a qualified state.	N/A
9.153 The ~~recommended~~ limits for airborne particle concentration in monitoring for each grade are given in Table 65. Table6 ~~5~~: ~~Recommended~~ **limits for airborne particle concentration for the monitoring of non-viable contamination**	9.15 The limits for environmental monitoring of airborne particle concentration for each graded area are given in Table 5. Table 5: Maximum permitted total particle concentration for monitoring.	13. In Grade A and B zones, the monitoring of the ≥5.0 μm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of ≥5.0 μm particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular

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Grade	~~Recommended~~ maximum limits for particles ≥ 0.5 μm/m³		~~Recommended~~ maximum limits for particles ≥ 5 μm/m³	
	in operation	at rest	in operation	at rest
A	3520	3520	2920	2920
B	352000	3520	2900	29
C	3520000	352000	29000	2900
D	Not defined(a) ~~Set a limit based on the risk assessment~~	3520000	Not defined(a) ~~Set a limit based on the risk assessment~~	29000

(a) For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and on historical data, where applicable.

Note 1: The particle limits given in the table for the “at rest” state should be achieved after a short “clean up” period (defined during qualification with a guidance value of 15 to 20 minutes) in an unmanned state ， after the completion of operations (refer to paragraph 4.30 and 4.31) ~~(see 5.26e)~~.

Note 2: With regards to the monitoring of 5.0 μm, the limit of 29 ~~20~~ is selected due to the limitations of monitoring equipment. Alert levels ~~It~~ should ~~be noted that alert limits~~ should ~~also~~ be set based on historical ~~and qualification~~ data, such that frequent sustained counts below the action limit which may be indicative of system contamination or deterioration should trigger an investigation. ~~such that frequent sustained recoveries below the action limit should also trigger an investigation~~. For the Grade A zone and Grade B area the importance of monitoring the ≥5 μm particulates is to identify negative trends as defined in the

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Grade	Maximum limits for total particle ≥ 0.5 μm/m³		Maximum limits for total particle ≥ 5 μm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined (a)	29 300	Not predetermined (a)

(a) For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and on routine data, where applicable.

Note 1: The particle limits given in the table for the “at rest” state should be achieved after a short “clean up” period defined during qualification (guidance value of less than 20 minutes) in an unmanned state, after the completion of operations (see paragraph 4.29).

Note 2: The occasional indication of macro particle counts, especially ≥ 5 μm, within grade A may be considered to be false counts due to electronic noise, stray light, coincidence loss etc.

However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration system, equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation.

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counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.

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manufacturer's CCS.		
9.164 For grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.	9.16 For grade A, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.	9. For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.
9.175 The grade A zone should be monitored continuously (for particulates ≥0.5 and ≥5 µm) and with a suitable sample flow rate ~~size~~ (at least 28 litres (a cubic foot) per minute) so that all interventions, transient events and any system deterioration ~~would be~~ is captured. The system should frequently correlate each individual sample result with the limits in Table 6 at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring. ~~and alarms triggered if alert limits are exceeded.~~	9.17 The grade A area should be monitored continuously (for particles ≥0.5 and ≥5 µm) and with a suitable sample flow rate (at least 28 litres ($1ft^3$) per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.	
9.186 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.~~	9.18 It is recommended that a similar system be used for the grade B area although the sample frequency may be decreased. The grade B area should be monitored at such a frequency and with suitable sample size that the programme captures any increase in levels of contamination and system	10. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be

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The grade B zone should be monitored at such a frequency and with suitable sample sizes that the programme captures any increase ~~change~~in levels of contamination and system deterioration. If alert limits are exceeded, alarms should be triggered.	deterioration. If alert levels are exceeded, alarms should be triggered.	determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.
~~9.17 The monitoring of grade C and D areas in operation should be performed in accordance with the principles of QRM to provide sufficient data to allow effective trend analysis. The requirements and alert/action limits will depend on the nature of the operations carried out.~~	N/A	15. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained.
9.19~~18~~ The selection of the monitoring system should take into account ~~of~~ any risk presented by the materials used in the manufacturing operation, for example those involving live organisms, powdery products or radiopharmaceuticals that may give rise to biological or chemical hazards.	9.19 The selection of the monitoring system should take into account any risk presented by the materials used in the manufacturing operation (e.g. those involving live organisms, powdery products or radiopharmaceuticals) that may give rise to biological, chemical or radiation hazards	11. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing. The selection of the monitoring

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		system should take account of any risk presented by the materials used in the manufacturing operation, for example those involving live organisms or radiopharmaceuticals.
9.2019 In the case where contaminants present due to the processes involved would damage the particle counter or present a hazard, （e.g. live organisms and radiological hazards）, the frequency and strategy employed should be such as to assure the environment classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriately defined intervals. The approach should be defined in the CCScontamination control strategy.	9.20 In the case where contaminants are present due to the processes involved and would potentially damage the particle counter or present a hazard (e.g. live organisms, powdery products and radiation hazards), the frequency and strategy employed should be such as to assure the environmental classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriate intervals. The approach should be defined in the CCS.	9. For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.
9.20 Where powdery products are manufactured, monitoring of particles may have to take into consideration an alternative monitoring scheme and frequency, e.g. monitoring for particle levels prior to and after the manufacturing process step.	N/A	
9.21 The sample sizes taken for monitoring purposes	9.21 The size of monitoring samples taken using automated	12. The sample sizes taken for

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using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal qualification of clean rooms and clean air devices. Monitoring sample volumes should be justified.	systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified.	monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean air devices.
~~9.22 Although monitoring of ≧ 5.0 μm particles are not required for room qualification and classification purposes, it is required for routine monitoring purposes as they are an important diagnostic tool for early detection of machine, equipment and HVAC failure.~~	N/A	13. In Grade A and B zones, the monitoring of the ≥5.0 μm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of ≥5.0 μm particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.
9.22~~23~~ The occasional indication of macro particle counts, especially ≧ 5.0 μm, may be considered false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration (HVAC) system, filling equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation.	9.15 Note2	
9.23~~24~~ 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 data generated during the initial qualification process, ongoing routine monitoring and periodic review of data ~~risk assessment~~.	N/A	N/A

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Environmental and personnel monitoring-viable particles ~~Viable monitoring~~	Environmental and personnel monitoring – viable particle	Clean room and clean air device monitoring
9.24~~25~~ Where aseptic operations are performed, microbiological monitoring should be frequent using a combination of methods such as settle plates, volumetric air, glove print 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.	9.22 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, 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. Cleanroom and equipment surfaces should be monitored at the end of an operation.	18. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation.
9.25~~26~~ Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of 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 critical interventions and on each exit from the grade B cleanroom ~~processing area.~~	转至新 9.25	
9.26 Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g. post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period), and in associated rooms that have not been used, in order to detect potential incidents of contamination which may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (i.e. cleaning and disinfection).	9.23 Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g. post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period), and in associated rooms that have not been used, in order to detect potential incidents of contamination which may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (e.g. cleaning and disinfection).	N/A

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9.27 Continuous monitoring in grade A zone ~~and B areas~~should be undertaken for the full duration of critical processing, including equipment (aseptic set up) assembly and filling operations . A similar approach should be considered for Grade B cleanrooms based on the risk of impact on the aseptic processing. ~~(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.	9.24 Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. 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.	18. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation.
9.25~~26~~ Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of 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 critical interventions and on each exit from the grade B cleanroom ~~processing area.~~	9.25 A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones. Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of 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 critical interventions (at a minimum gloves, but may require monitoring of areas of gown as applicable to the process) and on each exit from the grade B cleanroom (gloves and gown). Where monitoring of gloves is performed after critical interventions, the outer gloves should be replaced prior to	

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	continuation of activity. Where monitoring of gowns is required after critical interventions, the gown should be replaced before further activity in the cleanroom.	
N/A	9.26 Microbial monitoring of personnel in the grade A and grade B areas should be performed. Where operations are manual in nature (e.g. aseptic compounding or filling), the increased risk should lead to enhanced emphasis placed on microbial monitoring of gowns and justified within the CCS.	
N/A	9.27 Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular oversight by the quality unit (refer also to paragraph 8.19).	
9.28 The adoption of suitable rapid or automated monitoring systems should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methodology. ~~Rapid microbial monitoring methods may be adopted after validation as long as they are demonstrated to be at least equivalent to the established methodology.~~	9.28 The adoption of suitable alternative monitoring systems such as rapid methods should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods.	N/A
9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. The recovery efficiency of the sampling methods chosen should be qualified. ~~Sampling methods should not pose a risk of contamination to the manufacturing operations.~~	9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Supporting data for the recovery efficiency of the sampling methods chosen should be available.	18. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates).
~~9.30 Additional microbiological monitoring should also be performed outside production operations, e.g. after validation of systems, cleaning and disinfection.~~	N/A	Sampling methods used in operation should not interfere with zone protection. Results from monitoring

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<tr><td></td><td></td><td>should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation.</td></tr>
<tr><td>9.3031 ~~Recommended~~ action limits for microbial contamination are shown in Table 7
Table 7: ~~Recommended~~ maximum action limits for microbial contamination
<table>
<tr><th>Grade</th><th>Air sample cfu/m3</th><th>Settle plates (diam. 90 mm) cfu/4 hours (a)</th><th>Contact plates (diam. 55mm), cfu/ plate</th><th>Glove print, Including 5 fingers on both hands cfu/ glove</th></tr>
<tr><td>A (b)</td><td colspan="4">No growth(b) 1</td></tr>
<tr><td>B</td><td>10</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>C</td><td>100</td><td>50</td><td>25</td><td>-</td></tr>
<tr><td>D</td><td>200</td><td>100</td><td>50</td><td>-</td></tr>
</table>
(a) Settle plates should be exposed for the duration of operations and changed as required after 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used).Individual settle plates may be exposed for less than 4 hours. ~~Where settle plates are exposed for less than 4 hours the limits in the table should still be used. Settle plates should be exposed for the duration of critical operations and changed as required after 4 hours~~
(b)It should be noted that for Grade A, any growth should</td><td>9.30 Action limits for viable particle contamination are shown in Table 6
Table 6: Maximum action limits for viable particle contamination
<table>
<tr><th>Grade</th><th>Air sample CFU /m3</th><th>Settle plates (diam. 90 mm) CFU /4 hours(a)</th><th>Contact plates (diam. 55mm), CFU / plate(b)</th><th>Glove print, Including 5 fingers on both hands CFU / glove</th></tr>
<tr><td>A</td><td colspan="4">No growth(c)</td></tr>
<tr><td>B</td><td>10</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>C</td><td>100</td><td>50</td><td>25</td><td>-</td></tr>
<tr><td>D</td><td>200</td><td>100</td><td>50</td><td>-</td></tr>
</table>
(a) - Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used).
- For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM.
- Individual settle plates may be exposed for less than 4</td><td>19. Recommended limits for microbiological monitoring of clean areas during operation:
<table>
<tr><th colspan="5">Recommended limits for microbial contamination (a)</th></tr>
<tr><th>Grade</th><th>air sample cfu/m3</th><th>settle plates (diameter 90 mm) cfu/4 hours (b)</th><th>contact plates (diameter 55 mm) cfu/plate</th><th>glove print 5 fingers cfu/glove</th></tr>
<tr><td>A</td><td>< 1</td><td>< 1</td><td>< 1</td><td>< 1</td></tr>
<tr><td>B</td><td>10</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>C</td><td>100</td><td>50</td><td>25</td><td>-</td></tr>
<tr><td>D</td><td>200</td><td>100</td><td>50</td><td>-</td></tr>
</table>
Notes
(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.</td></tr>
</table>

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result in an investigation. ~~the expected result should be 0 cfu recovered; any recovery of 1 cfu or greater should result in an investigation.~~ (c) Contact plate limits apply to equipment room and gown surfaces within the Grade A zone and Grade B area. Routine gown monitoring is not normally required for Grade C and D areas, depending on their function. Note 1: It should be noted that the types of monitoring methods listed in the table above are examples and other methods can be used 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). Note 2: Limits are applied using cfu throughout the document. If different or new 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.	hours. (b) Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their function. (c) It should be noted that for grade A, any growth should result in an investigation. Note 1: It should be noted that the types of monitoring methods listed in the table above are examples and other methods can be used 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, aseptic processing, filling and lyophilizer loading). Note 2: Limits are applied using CFU throughout the document. If different or new 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.	
~~9.32 Monitoring procedures should define the approach to trending. Trends can include but are not limited to:~~ ~~a) Increasing numbers of action or alert limit breaches.~~ ~~b) Consecutive breaches or alert limits.~~ ~~c) Regular but isolated breaches of limits that may~~	N/A	N/A

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~~have a common cause, for example single excursions that always follow planned preventative maintenance.~~ ~~d) Changes in flora type and numbers.~~		
9.31~~33~~ Microorganisms detected in Grade A zone and Grade B area ~~If microorganisms are detected in 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 should~~may~~ also be given to the identification of grade C and D (for example where action limits or alert levels are exceeded or where atypical or potentially objectionable microorganisms are recovered). ~~contaminants and the requirements should be defined in the contamination control strategy.~~ The approach to organism identification and investigation should be documented.	9.31 Microorganisms detected in the grade A and grade B areas 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 following the isolation of organisms that may indicate a loss of control, deterioration in cleanliness or that may be difficult to control such as spore-forming microorganisms and moulds and at a sufficient frequency to maintain a current understanding of the typical flora of these areas.	N/A
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. Other surfaces should be monitored at the end of an operation.	9.25	N/A
9.33 Microbial monitoring of personnel in the Grade A zone and Grade B area should be performed to assess their aseptic behaviour. Where filling operations are manual in nature e.g. hand filling, the process in its entirety may be considered as one critical intervention. In these cases, the frequency of microbial monitoring of gowning should be based on scientific principles and justified as part of the CCS. Where monitoring is routinely	9.26&9.27	N/A

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performed by manufacturing personnel, consideration should be given to periodic monitoring under the supervision of the quality unit.		
Aseptic process simulation (APS) (also known as media fill)	Aseptic process simulation (APS) (also known as media fill)	Processing
9.34 Periodic verification of the effectiveness of the controls in place for aseptic processing should include a process simulation test using a sterile nutrient media and/or surrogate in place of the product ~~placebo~~. Selection of an appropriate nutrient media should be made based on the ability of the media and/or surrogate to imitate product characteristics at all processing stages. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. sterile aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized, etc.), alternative ~~surrogate~~ procedures that represent the operations as closely as possible can be developed and justified. Where surrogate materials, such as buffers, are used in parts of the process simulation, the surrogate material should not inhibit the growth of any potential contamination.	9.32 Periodic verification of the effectiveness of the controls in place for aseptic processing should include an APS using a sterile nutrient media and/or surrogate in place of the product. The APS should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient media and/or surrogate should be made based on the ability of the media and/or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the APS, the surrogate material should not inhibit the growth of any potential contamination.	66. Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill).Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.
9.35 The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps. Specifically:	9.33 The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:	67. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent

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i. ~~a)~~ Process simulation tests should assess all aseptic operations performed subsequent to the sterilisation and decontamination cycles of materials utilised in the process to the point where the container is sealed.~~of materials utilised in the process.~~ ii. ~~b)~~ For non-filterable formulations any additional aseptic steps should be assessed. iii. ~~c)~~ Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended. ~~Aseptic manufacturing performed in a strict anaerobic environment should be evaluated with an anaerobic media in addition to aerobic evaluation.~~ iv. ~~d)~~ Processes requiring the addition of sterile powders should use ~~employ~~ an acceptable surrogate material in containers identical to those ~~utilized~~ used in the process ~~being~~ under evaluated. v. ~~e)~~ Separate simulations of individual unit operations (e.g. processes involving drying, blending, milling and subdivision of a sterile powder) should generally be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process. ~~Processes involving blending, milling and subdivision of a sterile powder require similar~~	i. The APS should assess all aseptic operations performed subsequent to the sterilisation and decontamination cycles of materials utilised in the process to the point where the container is sealed. ii. For non-filterable formulations, any additional aseptic steps should be assessed. iii. Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended. iv. Processes requiring the addition of sterile powders should use an acceptable surrogate material in the same containers as those used in the process under evaluation. v. Separate simulations of individual unit operations (e.g. processes involving drying, blending, milling and subdivision of a sterile powder) should be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process. vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters.	manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations.

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~~attention.~~ vi. ~~f)~~ The process simulation test for lyophilized products should include 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. ~~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.~~ vii. The lyophilization process simulation should duplicate all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling-over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable: • The use of air to break vacuum instead of nitrogen. • Replicating the maximum interval between sterilization of the lyophilizer and its use. • Replicating the maximum period of time between sterilization and lyophilization. • Quantitative aspects of worst case situations, e.g. loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the	vii. The lyophilization process simulation should mimic all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling-over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable: • The use of air to break vacuum instead of nitrogen or other process gases. • Replicating the maximum interval between sterilisation of the lyophilizer and its use. • Replicating the maximum period of time between filtration and lyophilization. • Quantitative aspects of worst-case situations, e.g. loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.	

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environment.		
9.36 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: i. ~~a)~~ Inherent interventions representative of the routine process at the maximum accepted frequency per number of filled units(e.g. loading of vials into a lyophilizer). ii. ~~b)~~ Corrective interventions，that occur frequently during routine production, in representative number and with the highest degree of intrusion(e.g. correcting jammed stoppers). ~~acceptable~~.	9.34 The APS should take into account various aseptic manipulations and interventions known to occur during normal production as well as worst-case situations, and take into account the following: i. Inherent and corrective interventions representative of the routine process should be performed in a manner and frequency similar to that during the routine aseptic process. ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility.	N/A
N/A	9.35 APS should not be used to justify practices that pose unnecessary contamination risks.	N/A
9.37 Interventions should not be designed or selected to justify poor process or facility design or to assess unacceptable interventions that rarely occur and which should lead to a thorough investigation and product assessment when they do occur. ~~There should be an approved list of allowed interventions, both inherent and corrective, which may occur during production and in the APS. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be updated, as necessary, to ensure consistency with the actual manufacturing activities.~~	N/A	N/A
9.38 In developing the process simulation test plan, ~~risk management principles should be used and~~ consideration should be given to the following: i. ~~a)~~ Identification of worst case conditions covering	9.36 In developing the APS plan, consideration should be given to the following: i. Identification of worst case conditions covering the	N/A

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the relevant variables and their microbiological impact on the process. The outcome of the assessment should justify the variables selected.	relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment should justify the variables selected.	
ii. ~~b)~~ Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or a matrix approach may ~~can~~ be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified ~~initial validation of the same container/closure configuration~~.	ii. Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified.	
iii. ~~c)~~ The volume filled per container, which should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product. The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.	iii. Maximum permitted holding times for sterile product and equipment exposed during the aseptic process. iv. The volume filled per container, which should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product. The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.	
iv. ~~d)~~ Maximum permitted holding times for sterile product and associated sterile components exposed during the aseptic process. 【*移至 9.36 point iii*】	v. The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air unless anaerobic simulation is intended. In these situations, inclusion of occasional anaerobic simulations as part of the overall validation strategy should be considered (see paragraph 9.33 point iii).	
v. ~~e)~~ The method of detection of microbial contamination should be scientifically justified to ensure ~~Ensuring~~ that any contamination is detectable. 【*移至 9.36 point vii*】		
vi. The selected nutrient media should be capable of	vi. The selected nutrient media should be capable of	

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growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates and supporting recovery of low numbers of these microorganisms.	growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates.	
vii. ~~f)~~The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air, unless anaerobic simulation is intended. In these situations, inclusion of occasional anaerobic simulations as part of the overall validation strategy should be considered (refer to paragraph 9.35 point iii). 【*移至 9.36 point v*】	vii. The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.	
viii. ~~g)~~The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product. ~~The duration of the process simulation filling run to ensure it is conducted over the maximum permitted filling time. If this is not possible, then the run should be of sufficient duration to challenge the process, the operators that perform interventions, and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.~~	viii. The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.	
ix. Where the manufacturer operates different shifts then the APS should be designed to capture specific factors (e.g. for those manufacturing during a night or	ix. Where the manufacturer operates different or extended shifts, the APS should be designed to capture factors specific to those shifts that are assessed to pose a risk to product sterility, for example the maximum duration for which an operator may be present in the cleanroom.	
	x. Simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment).	
	xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.	

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extended shift, fatigue should be considered). x. ~~h)~~ Simulating normal aseptic manufacturing interruptions where the process is idle(e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment, etc.).. ~~In these cases, environmental monitoring should be conducted to ensure that grade A conditions have been maintained.~~ xi. ~~i)~~ Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation. ~~The special requirements and considerations for manually intensive operations.~~ xii. ~~j)~~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, ~~If end of production campaign APS are used, then~~ it should be demonstrated that any residual product does not negatively impact the recovery of any potential	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. xiii. 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.	

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microbiological contamination. 【*此条拆分为 9.36 point xii&xiii*】 ~~k）Where barrier technologies (RABS, isolators, BFS, etc.) are used in the routine aseptic manufacturing process, the relative risk and unique aspects of these technologies should be taken into consideration when assessing the design of aseptic process simulation tests.~~		
9.39 For sterile active substances, batch sizes should be large enough to represent routine operation, simulate intervention operation at the worst case, and cover potential contact surfaces. In addition, all the simulated materials (surrogates of growth medium) should be subjected to microbiological evaluation. The ~~recovery rate from~~ simulation materials should be sufficient to satisfy the evaluation of the process being simulated and should not compromise the recovery of micro-organisms.	9.37 For sterile active substances, batch size should be large enough to represent routine operation, simulate intervention operation at the worst case, and cover all surfaces that may come into contact with the sterile product. In addition, all the simulated materials (surrogates or growth medium) should be subjected to microbial evaluation. The simulation materials should be sufficient to satisfy the evaluation of the process being simulated and should not compromise the recovery of micro-organisms.	N/A
9.40 Process simulation tests should be performed as initial validation, ~~generally~~ with at last three consecutive satisfactory simulation tests that cover all working shift that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment (e.g. modification to the HVAC system, equipment, major facility shut down, changes to process, number of shifts and numbers of personnel etc.). Normally process simulation tests (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process and filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given	9.38 APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment which are assessed to have an impact on the sterility assurance of the product (e.g. modification to the HVAC system, equipment, changes to process, number of shifts and numbers of personnel, major facility shut down). Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to	68. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process.

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to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.	performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.	
9.41 Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each shift. ~~Where manual filling occurs, each product, container closure, equipment train and operator should be revalidated approximately every 6 months.~~ The APS batch size should mimic that used in the routine aseptic manufacturing process. ~~An aseptic process or filling should be subject to a repeat of the initial validation when:~~ ~~a) Revalidation of the unique process has failed and corrective actions have been taken.~~ ~~b) The specific aseptic process has not been in operation for an extended period of time.~~ ~~c) A change to the process, equipment, personnel, procedures or environment that has potential to affect the aseptic process or the addition of new product containers or container closure combinations.~~	9.39 Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each operator. The APS batch size should mimic that used in the routine aseptic manufacturing process.	N/A
9.42 The number of units processed (filled) for process simulation tests should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process; justification for the number of units to be filled should be clearly captured in the PQS. Typically, a minimum of 5000 to 10000 units are filled. For small batches, e.g. those under 5,000 units filled, the number of containers for media fills should at least equal	9.40 The number of units processed (filled) for APS should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the CCS. Typically, a minimum of 5000 to 10000 units are filled. For small batches (e.g. those under 5000 units), the number of containers for APS should at least equal the size of the production batch.	69. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply: ♦ When filling fewer than 5000 units,

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the size of the production batch.		no contaminated units should be detected. • When filling 5,000 to 10,000 units: a) One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill; b) Two (2) contaminated units are considered cause for revalidation, following investigation. • When filling more than 10,000 units: a) One (1) contaminated unit should result in an investigation; b) Two(2) contaminated units are considered cause for revalidation, following investigation.
~~9.43 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.~~	转至 9.46	
9.43 Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container. Units with Cosmetic defects, or those who have gone through non-destructive in process control checks ~~non-destructive weight checks and all other units~~ should be identified and incubated ~~with the other units~~. Units discarded during the process simulation and not incubated should be comparable to units discarded during a routine fill. Examples may include those normally discarded after the set-up process or due to an intervention or where the integrity of the unit is compromised as would be identified by the routine inspection process for the product.	9.41 Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container. All integral units from the APS should be incubated and evaluated, including units with cosmetic defects or those which have gone through non-destructive in-process control checks. If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production SOPs clearly specify that units must be removed under the same circumstances (i.e. type of intervention; line location; specific number of units removed). In no case should more units be removed during a media fill intervention than would be cleared during a production run. Examples may include those that must be discarded during	N/A

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	routine production after the set-up process or following a specific type of intervention. To fully understand the process and assess contamination risks during aseptic setup or mandatory line clearances, these units would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.	
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.	9.42 Where processes include materials that contact the product contact surfaces but are then discarded (e.g. product flushes), 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.	N/A
9.45 Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (i.e. amber glass, opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. 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 conditions and duration ~~and temperature~~ should be scientifically justified and validated to provide an appropriate ~~for the process being simulated and the selected growth medium~~ level of sensitivity of detection of microbial contamination. *【涂色部分转至9.44】*	9.43 Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (e.g. amber glass, opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. Microorganisms isolated from contaminated units should be identified to the species level when practical, to assist in the determination of the likely source of the contaminant.	N/A
9.46 Filled APS units should be incubated without	9.44 Filled APS units should be incubated without unnecessary	N/A

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unnecessary delay to achieve the best possible recovery of potential contamination.	delay to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination.	
9.47 On completion of incubation: i. Filled APS units should be inspected by staff, who have been trained and qualified in the visual inspection procedures, under conditions similar to those for visual inspection, that facilitate the identification of any microbial contamination. ii. Samples of these units should undergo positive control by inoculation with a suitable range of reference organisms and local isolates.	9.45 On completion of incubation: i. Filled APS units should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination. Inspection should be conducted under conditions that facilitate the identification of any microbial contamination. ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.	N/A
9.4843The 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.~~ a failed process simulation and the following actions should occur:	9.46 The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken: i. An investigation to determine the most probable root cause(s). ii. Determination and implementation of appropriate corrective measures. iii. A sufficient number of successful, consecutive repeat APS (normally a minimum of 3) should be conducted in order to demonstrate that the process has been returned to a state of control.	70. For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

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i. An investigation to determine the most probable root causes. ii. Determination and implementation of appropriate corrective measures. 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. iv. A prompt review of all appropriate records relating to aseptic production since the last successful APS. The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful process simulation. All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome. v. All products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred. vi. Production should resume only after completion of successful revalidation.	iv. A prompt review of all appropriate records relating to aseptic production since the last successful APS. a) The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS. b) All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome. v. All products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred. vi. Where the root cause investigation indicates that the failure was related to operator activity, actions to limit the operator's activities, until retrained and requalified, should be taken. vii. Production should resume only after completion of successful revalidation.	
~~9.46 All products that have been manufactured on a line subsequent to the process simulation should be~~	N/A	N/A

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~~quarantined until a successful resolution of the process simulation has occurred.~~		
~~9.47 In the case of a failed process simulation there should be a prompt review of all appropriate records relating to aseptic production since the last successful process simulation. The outcome of the review should include a risk assessment of the non-sterility for batches manufactured since the last successful process simulation, and the justification for the disposition of batches of product affected. Subsequent to a failed APS, in addition to a full investigation, production should resume only upon further successful APS unless adequately justified. The number of repeat successful APS prior to resuming production should also be justified.~~	N/A	70. For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.
N/A	9.47 All APS runs should be fully documented and include a reconciliation of units processed (e.g. units filled, incubated and not incubated). Justification for filled and non-incubated units should be included in the documentation. All interventions performed during the APS should be recorded, including the start and end time of each intervention and the involved person. All microbial monitoring data as well as other testing data should be recorded in the APS batch record.	N/A
N/A	9.48 An APS run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. An investigation should be documented in such cases.	N/A
9.49 APS should be carefully observed by personnel with specific expertise in aseptic processing to assess the correct performance of operations and address inappropriate practices if detected.	N/A	N/A
9.50~~48~~ Where results indicate that an operator may have	N/A	N/A

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failed qualification, actions to restrict entry of the operator to the aseptic processing areas should be taken.		
9.51 An aseptic process or filling should be subject to a repeat of the initial validation when: i. The specific aseptic process has not been in operation for an extended period of time. ii. There is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container closure combinations.	9.49 An aseptic process should be subject to a repeat of the initial validation when: i. The specific aseptic process has not been in operation for an extended period of time. ii. There is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations.	N/A
9.~~49~~ 52 All process simulation runs should be fully documented and include a reconciliation of units processed (e.g. units filled, incubated, not incubated, and rejected). ~~and changes in the custody of the APS batch~~. All interventions performed during the process simulations should be recorded, including the start and end of each intervention. All microbial monitoring data as well as other testing data should be recorded in the APS batch record.	转至 9.47	N/A

10. Quality control (QC)

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10.1 ~~Microbiological contamination~~ It is important that there are personnel with appropriate training and experience in microbiology and knowledge of ~~starting materials should be minimal.~~ the process to support the design of the manufacturing process, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.	10.1 There should be personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.	Processing 74. Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.
10.2 Specifications for raw materials, components and products should include requirements for ~~microbiological~~ microbial quality when the need for this has been indicated by monitoring and/or by the ~~contamination control strategy~~ CCS.	10.2 Specifications for raw materials, components and products should include requirements for microbial, particulate and endotoxin/pyrogen limits when the need for this has been indicated by monitoring and/or by the CCS.	N/A
10.~~2~~3 The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilized products and the results considered as part of the final batch review. There should be ~~working~~ defined limits ~~on contamination~~ for bioburden immediately before the sterilizing filter or the terminal sterilization process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst case scenario (e.g. at the end of hold time). Where overkill sterilization parameters are set for terminally sterilized products, bioburden should be monitored at suitable scheduled intervals.	10.3 The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products and the results considered as part of the final batch review. There should be defined limits for bioburden immediately before the final sterilising grade filter or the terminal sterilisation process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst-case scenario (e.g. at the end of hold time). Where overkill sterilisation parameters are set for terminally sterilised products, bioburden should be monitored at suitable scheduled intervals.	Processing 80. The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate the level of endotoxins should be monitored. All

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		solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.
10.4 ~~For~~A pre-sterilization bioburden monitoring program for the product and components should be developed to support parametric release ~~systems,~~. The bioburden ~~assay~~ should be performed ~~on~~ for each batch ~~and considered as an in-~~. The sampling locations of filled units before sterilization should be based on a worst case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilizing process ~~test.~~ determined. Where appropriate, the level of pyrogen (endotoxins) should be monitored.	10.4 For products authorised for parametric release, a supporting pre-sterilisation bioburden monitoring programme for the filled product prior to initiating the sterilisation cycle should be developed and the bioburden assay should be performed for each batch. The sampling locations of filled units before sterilisation should be based on a worst case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilising process determined. Where appropriate, the level of endotoxin/pyrogen should be monitored.	Quality control 126. In those cases where parametric release has been authorised, special attention should be paid to the validation and the monitoring of the entire manufacturing process.
10.5 The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or qualification parameters. The test should be validated for the product~~(s)~~ concerned.	10.5 The sterility test applied to the finished product should only be regarded as the last in a series of critical control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or validation parameters. The test should be validated for the product concerned.	Quality control 125. The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.
10.6 The sterility test should be performed under aseptic conditions~~, which are at least consistent with the standard of clean room required for the aseptic manufacture of pharmaceutical products.~~ ~~10.7~~ Samples taken for sterility testing should be representative of the whole of the batch~~,~~ but should in particular include samples taken from parts of the batch considered to be most at risk of contamination,	10.6 The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example: i. For products which have been filled aseptically, samples should include containers filled at the beginning and end of	127. Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.: a. for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and

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for example: ~~a)~~ 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. ~~b)~~ ii For products which have been heat sterilized in their final containers, ~~consideration~~ samples taken should be ~~given to taking samples from~~ representative of the worst case locations (e.g. the potentially coolest or slowest to heat part of ~~the~~ each load~~.~~). ~~c) Each sterilized load should be considered as different batches and require a separate sterility test.~~ ~~d)~~ iii For products that ~~have been~~ are lyophilized ~~in~~, samples taken from different lyophilization loads。 Note: Where ~~sterilization or lyophilization leads to separate sterility tests,consideration of~~ the manufacturing process results in sub-batches (e.g. for terminally sterilized products) then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests ~~should also be given~~.	the batch. Additional samples, e.g. taken after critical interventions should be considered based on risk. ii. For products which have been heat sterilised in their final containers, samples taken should be representative of the worst case locations (e.g. the potentially coolest or slowest to heat part of each load). iii. For products which have been lyophilized, samples taken from different lyophilization loads. Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilised products) then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests.	after any significant intervention, b. or products which have been heat sterilised in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

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10.7 For some products it may not be possible to perform a sterility test prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the CCS should clearly capture the identified risks, the additional considerations of design of the process and additional monitoring required to mitigate the identified risks.	10.7 For some products it may not be possible to obtain a sterility test result prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the additional considerations of design of the process and additional monitoring and/or alternative test methods required to mitigate the identified risks should be assessed and documented.	N/A
10.8 Any process (e.g. ~~VHP~~ Vaporized Hydrogen Peroxide or VH202, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method.	10.8 Any process (e.g. Vaporized Hydrogen Peroxide, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the sample.	N/A
10.9 Media used for environmental monitoring and APS should be tested for its growth promotion capability, in accordance with a formal written program.	10.9 Media used for product testing should be quality control tested according to the related Pharmacopeia before use. Media used for environmental monitoring and APS should be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative local isolates. Media quality control testing should normally be performed by the end user. Any reliance on outsourced testing or supplier testing of media should be justified and transportation and shipping conditions should be thoroughly considered in this case.	N/A
10.10 Environmental monitoring data and trend data generated ~~in grade A and B~~ for classified areas should be reviewed as part of product batch ~~release.~~ 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 ~~out~~ exceeding the established limits. For products	10.10 Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification/release. A written procedure 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	N/A

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with short shelf life, the environmental data for the time of ~~specification~~ manufacture may not be available; in these cases, the certification should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid monitoring systems.	manufacture may not be available; in these cases, the compliance should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid/alternative methods.	
10.11 Where rapid and automated microbial methods ~~can also be considered.~~ are used for general manufacturing purposes, these methods should be validated for the product(s) or processes concerned ~~and be approved in the registered product testing specification~~.	10.11 Where rapid and automated microbial methods are used for general manufacturing purposes, these methods should be validated for the product(s) or processes concerned.	N/A