European Commission

康利华咨询
A Tigermed Company

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION

VOLUME 4 EU GUIDELINES FOR GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE

欧盟药品管理原则

第四卷 人用和兽用药品生产质量管理规范

ANNEX 1

附录 1

MANUFACTURE OF STERILE MEDICINAL PRODUCTS（FINAL VERSION）

无菌药品生产（正式版）

25th
SINCE1998
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北京康利华咨询服务有限公司成立于1998年，是一家专业从事药品法规符合方面服务的咨询公司。康利华致力于国内外药政法规研究以及前沿信息搜索、追踪实践，特别是中、美、欧药品法规符合的咨询，目前已成为中国业内规模最大、业绩最多、最为专业的咨询公司之一。

二十多年来，康利华在咨询师队伍、服务标准、服务规程、项目管理、保密体系等方面形成了成熟、规范的服务体系，并且连续多年通过ISO 9001质量管理体系认证，累计为超过1370家中外客户提供了专业的服务，受到了客户的广泛肯定和赞誉。

2014年，北京康利华咨询服务有限公司被**泰格医药**（股票代码:300347.SZ/3347.HK）收购。康利华与泰格集团和兄弟公司一起，共同组成一个覆盖药品从研发到生产的全产业链的综合型CRO公司，为国内外客户提供一个从研发、注册、转化到生产的一站式服务平台，进一步拓展了康利华在医药研发与注册、GMP符合与验证测试等领域的综合与整体服务能力。

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GMP合规咨询

康利华咨询致力于为全球制药企业提供覆盖药品生命周期的GMP合规咨询服务，以满足客户在研发、注册、上市等不同阶段质量管理体系的合规需求

中国GMP合规咨询	美国FDA cGMP咨询	GMP符合性审计	新工厂建设合规解决方案
欧盟EU GMP咨询	第三方GxP审计	研发质量体系建立	澳大利亚TGA GMP咨询
差距分析/模拟审计	NMPA境外检查支持	WHO PQ咨询	会议&培训

以NMPA、FDA、EMA、PIC/S、TGA、WHO-PQ等相关法规要求为基础，提供包括研发质量管理体系建立、技术转移合规指导、数据完整性审核、MAH体系搭建、新建药厂整体解决方案、国内外GMP符合性审计、差距分析、模拟审计、迎检指导、现场或远程检查支持、定制化培训等方面服务内容，确保客户产品符合目标市场的GMP法规要求。

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- 受托企业合规审计
- 物料供应商合规审计
- 受托企业合规审计

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欧盟的仿药的 ANDA 申请和原辅包 CEP、ASMF 申请等。

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全面生产管理平台

整体解决方案　完整实施交付

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实验室信息管理	LIMS	质量管理	QMS
实验室执行	LES	文档管理	DMS
科研信息管理	RDMS	培训管理	TMS
电子实验记录	ELN		

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生产制造管理		数字化管控	
生产执行管理	MES	数据采集	SCADA
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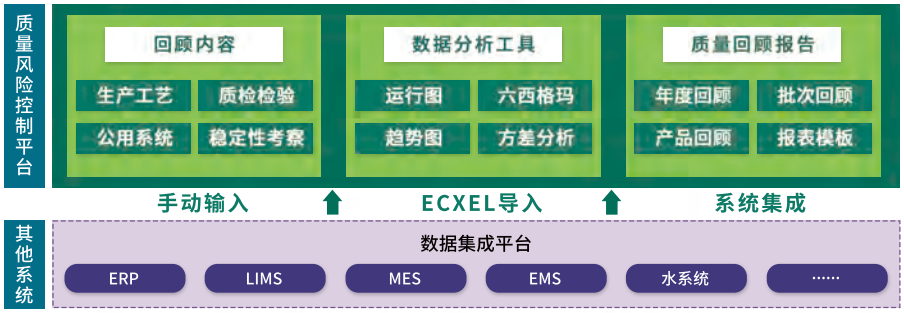

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The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

欧盟药品管理原则 第四卷 人用和兽用药品生产质量管理规范

Annex 1
附录 1

Manufacture of Sterile Medicinal Products
无菌药品生产

Legal context for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation 2019/6 on the Community code relating to veterinary medicinal products. This document provides technical guidance on the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Commission Directive (EU) 2017/1572 for medicinal products for human use, Directive 91/412/EEC for veterinary use, and Commission Delegated Regulation (EU) 2017/1569 for investigational medicinal products for human use and arrangements for inspections supplementing Regulation (EU) No 536/2014 on clinical trials.

该详细指导原则发布的法律背景：该详细指导原则发布的法律背景：关于人用药品指令 Directive 2001/83/EC 第 47 条和关于兽药产品法规 Regulation 2019/6 第 47 条。本文件为药品生产质量管理规范(GMP)的原则和指南提供了技术指导，这些原则和指南包括人用药品指令 Commission Directive (EU) 2017/1572、兽药指令 Directive 91/412/EEC 和人用临床试验药品授权法规 Commission Delegated Regulation (EU) 2017/1569，以及补充临床试验法规 Regulation (EU) No 536/2014 的检查安排。

This Annex is intended to assist national authorities in the application of the EU legislation. Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

本附录旨在协助各国主管当局实施欧盟法律。仅欧盟法院有权对欧盟法律进行权威解释。

Status of the document: Revision of the 2007 version of Annex 1.

文件状态：2007 年版附录 1 的修订版

说明 1：本文原文来源于欧盟官方网站：https://health.ec.europa.eu/medicinal -products/eudralex/eudralex-volume -4_en

说明 2：翻译时间有限，若有翻译不足之处还望各位指正！勘误可联系：

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Document History：

文件历史：

Previous version dated 30 May 2003, in operation since 上一版本日期为 2003 年 5 月 30 日，生效日期为	September 2003 2003 年 9 月
Revision to align classification table of clean rooms, to include guidance on media simulations, bioburden monitoring and capping of vials 修订以校正洁净室分级表，包括培养基模拟灌装、生物负载监测和西林瓶轧盖的相关指导原则。	November 2005 to December 2007 2005 年 11 月至 2007 年 12 月
Date for coming into operation and superseding 生效及替换日期	01 March 2009/01 March 2010 2009 年 3 月 1 日/2010 年 3 月 1 日 Note: Provisions on capping of vials were implemented on 01 March 2010. 备注：关于西林瓶轧盖的相关规定执行日期为 2010 年 3 月 1 日

Reasons for changes: The GMP/GDP Inspectors Working Group and the PIC/S Committee jointly recommend that the current version of annex 1, on the manufacture of sterile medicinal products, is revised to reflect changes in regulatory and manufacturing environments. The new guideline should clarify how manufacturers can take advantage of new possibilities deriving from the application of an enhanced process understanding by using innovative tools as described in the ICH Q9 and Q10 guidelines.

The revision of Annex 1 should also take into account related changes in other GMP chapters and annexes as well as in other regulatory documents. The revised guideline will seek to remove ambiguity and inconsistencies and will take account of advances in technologies.

变更原因：GMP/GDP 检查员工作组和 PIC/S 委员会联合建议，对当前版本的关于无菌药品生产的附件 1 进行修订，以反映监管和生产环境的变化。新指南应阐明制造商如何通过使用 ICH Q9 和 Q10 指南中所述的创新工具，增强工艺理解并带来新的可能性。

附件 1 的修订还应考虑到 GMP 其他章节和附件以及其他法规文件中的相应变化。修订后的指导原则将设法消除不明确和不一致的地方，并将考虑到技术的进步。

Deadline for coming into operation:

生效的最终期限：

–25 August 2023: one year from the date of publication in Eudralex Volume 4

–2023 年 8 月 25 日：Eudralex 第四卷发布日期后 1 年

–25 August 2024: two years from the date of publication in Eudralex Volume 4 for point 8.123

–2024 年 8 月 25 日：针对 8.123 条款为 Eudralex 第四卷发布日期后 2 年

说明 1：本文原文来源于欧盟官方网站：https://health.ec.europa.eu/medicinal –products/eudralex/eudralex –volume –4_en

说明 2：翻译时间有限，若有翻译不足之处还望各位指正！勘误可联系：

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条目变化汇总表

Final –20220825 **（总计 293 条）**	**Current Annex 1 –2008** **（总计 127 条）**	**Current Annex 1 –2008 对应的条款号**
1. Scope 范围	N/A	N/A
2. Principle 总则（7 条）	Principle	Principle，71，82
3. Pharmaceutical Quality System (PQS) 制药质量体系（PQS）（2 条）	N/A	N/A
4. Premises 厂房（36 条） • Barrier Technologies • Cleanroom and clean air equipment qualification • Disinfection	• Premises • Clean room and clean air device classification • Isolator technology • Sanitation	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
5. Equipment 设备（9 条）	Equipment	6，11，56，57，58，60
6. Utilities 公用系统（22 条） • Water systems • Steam used as a direct sterilising agent • Gases and vacuum systems • Heating and cooling and hydraulic systems	N/A	49，59，72，96
7. Personnel 人员（18 条）	Personnel	36，37，38，39，40，41，42，43，44，45，73
8. Production and specific technologies 生产与专项技术（139 条） • 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	• 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	17，26，27，28，29，30，31，32，33，34，35，64，65，76，77，78，79，81，83，84，85，86，87，88，89，90，91，92，93，94，95，97，98，99，100，101，102，103，104，105，106，107，108，109，110，111，112，113，114，115，116，117，118，119，120，121，122，123，124

• 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)	sterilised in their final container • Finishing of sterile products	
9. Environmental and process monitoring 环境及工艺监测（49 条） • General • Environmental and process monitoring • Environmental monitoring – total particle • Environmental and personnel monitoring – viable particle • Aseptic process simulation (APS) (also known as media fill)	• Clean room and clean air device classification • Clean room and clean air device monitoring • Processing	8，9，10，11，12，13，15，18，19，20，66，67，68，69，70
10. Quality control (QC)质量控制（QC）（11 条）	Quality control	74，80，125，126，127
11. Glossary 术语	N/A	N/A

Documentation Map：
文档结构

Section Number 章节号	General overview 总览
1. Scope 范围	Includes additional areas (other than sterile products) where the general principles of the annex can be applied. 包含额外部分（除无菌以外的部分）指适用于附录总则的部分
2. Principle 总则	General principles as applied to the manufacture of sterile products. 适用于无菌产品的一般原则。
3. Pharmaceutical Quality System (PQS) 制药质量体系（PQS）	Highlights the specific requirements of the PQS when applied to sterile products. 强调了当适用于无菌产品时的 PQS 的具体要求。
4. Premises 厂房	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Barrier Technology. 有关厂房设计的具体需求的总体指导以及包括隔离技术使用的厂房确认的指导。
5. Equipment 设备	General guidance on the design and operation of equipment. 设备设计和操作的总体指导。
6. Utilities 公用系统	Guidance regarding the special requirements of utilities such as water, gas and vacuum. 有关诸如水系统，气体系统以及真空系统等公用工程系统的特殊要求的指导。
7. Personnel 人员	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance regarding the qualification of personnel. 提供了业务培训、专业知识和技能需求的指导，同时给予人员资质方面的指导。
8. Production and specific technologies 生产与专项技术	Guidance on the approaches to be taken regarding aseptic and terminal sterilization processes. Guidance on the approaches to sterilization of products, equipment and packaging components. Also guidance on different technologies such as lyophilization and Form –Fill –Seal where specific requirements apply.

	对非最终灭菌工艺和最终灭菌工艺方法提供指导；对产品、设备以及包装部件的灭菌方法提供指导。同时对不同的技术，如冻干和成型 –灌 –封等特定要求的应用提供指导；
9. Environmental and process monitoring 环境及工艺监测	This section differs from guidance given in section 4 in that the guidance here applies to ongoing routine monitoring regarding the design of systems and setting of action limits alert levels and reviewing trend data. 与本指南中第四节不同，本节适用于持续的常规监测，包括系统的设计、设置行动限以及分析趋势数据。 The section also gives guidance on the requirements of Aseptic Process Simulation (APS). 本部分同样对无菌工艺的模拟提供了指导。
10. Quality control (QC) 质量控制（QC）	Guidance on some of the specific Quality Control requirements relating to sterile products. 对关于无菌产品具体的质量控制要求提供指导。
11. Glossary 术语	Explanation of specific terminology. 具体专业名词的解释。

1. Scope 范围

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.
无菌产品的生产涵盖了各种无菌产品类型（活性成分，辅料，内包材和制剂），包装规格（从单剂量到多剂量），工艺（从高度自动化系统到人工操作）和技术（如生物技术，传统小分子生产系统以及密闭系统）。本附录提供了采用质量风险管理（QRM）原则对所有无菌产品的生产中使用的设施、设备、系统和程序进行设计和控制时应该遵循的总体指导原则，以确保成品免受微生物，微粒和内毒素/热原污染。

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.
质量风险管理适用于本文全篇，通常不会在特定段落中提及。文中给出的特定限度、频次或范围应视为最低要求。它们是由以前发现的问题的历史监管经验而在文中进行规定的，这些问题已经影响到患者的安全。

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 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.
本附录旨在为无菌产品的生产提供指导。然而，有些原则和指导（例如污染控制策略、厂房设计、洁净室分级、确认、验证、监测和人员更衣）或许可用于支持其他不需要灭菌，但需要控制和降低微生物、微粒和内毒素/热原污染的产品的生产（如某些液体，乳膏，软膏以及低微生物负载的生物制品中间产品）。如果生产商选择将本指南应用于非无菌产品，生产商应明确记录所应用的原则，并认可应证明符合这些原则。

2. Principle 原则

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:

无菌产品的生产应符合一些特殊要求，以尽量降低微生物、微粒及内毒素/热原污染的风险。应考虑以下关键领域：

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.

设施、设备及工艺应按照药品生产质量管理规范（GMP）指导原则相关章节进行适当的设计、确认和/或验证，在适用的情况下，应进行持续性确认。应考虑使用适当的技术（如限制进入屏障系统（RABS））、隔离器、机器人系统、快速/替代方法和连续监测系统）），以加强对产品的保护，使其免受人员、物料和周围环境等潜在的内毒素/热原、微粒和微生物的外来污染源的影响，并协助快速检测环境和产品中的潜在污染物。

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.

在生产、包装和分销的过程中，根据特别关注的涉及保护无菌产品的原则，人员应具有充分的资质、经验、培训和态度。

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.

无菌产品生产所用的工艺和监测系统应该由具有适当的工艺、工程和微生物知识的人员进行设计、调试、确认、监测并定期回顾。

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.

应对原料和包装材料进行充分的控制和检测，以确保其微生物负载和内毒素/热原水平适合其预期用途。

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.
应按照 QRM 的原则对工艺、设备、设施和生产活动进行管理，从而为识别、科学评估和控制潜在的质量风险提供一种主动的方法。在使用替代方法时，应以适当的原理、风险评估和缓解措施作为支持，并应符合本附录的意图。

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.
首先 QRM 的重点应包括对设施、设备和工艺进行适当的设计，然后执行良好设计的程序，最后以监测系统作为要素，证明设计和程序已经得到正确执行，并继续按照预期执行。单纯的监测或检验并不能保证无菌性。

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.
应在整个设施内实施污染控制策略（CCS）以确定所有关键控制点，并评估用于管理药品质量和安全风险的所有控制措施（设计、程序、技术和组织机构）和监测措施的有效性。CCS 的组合策略应建立起稳健的污染预防保障措施。应积极审核并酌情更新 CCS，并应推动生产和控制方法的持续改进。其有效性应成为周期性管理评审的一部分。如果现有的控制系统已经到位并得到了适当的管理，这些系统可能不需要更换，但应在 CCS 中提及，并理解各系统之间的相关互动关系。

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.
污染控制和为最大限度地减少来自微生物、内毒素/热原和微粒等来源的污染风险而采取的步骤包括一系列相互关联的事件和措施。它们通常是单独进行评估、控制和监测的，但应综合考虑其总体效力。

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).
Elements to be considered within a CCS should include (but are not limited to):
制定 CCS 需要详细的技术和工艺知识。潜在的污染源可归结为微生物和细胞碎片（如热原、内毒素）以及颗粒物（如玻璃和其他可见异物和不溶性微粒）。
在 CCS 中要考虑的要素应包括（但不限于）：

i. Design of both the plant and processes including the associated documentation.
厂房和工艺的设计，包括相关的文件。

ii. Premises and equipment.
厂房和设备

iii. Personnel.
人员

iv. Utilities.
公用工程

v. Raw material controls – including in –process controls.
原料控制 –包含过程控制

vi. Product containers and closures.
产品容器和密封系统

vii. Vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers.
供应商批准 - 如关键部件供应商、无菌组件和一次性系统（SUS），以及关键服务供应商。

viii. Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services.
外包活动的管理和关键信息的可获得性/在各方间的转移，如委托灭菌服务。

ix. Process risk management.
工艺风险管理

x. Process validation.

工艺验证

xi. Validation of sterilisation processes.
灭菌工艺验证

xii. Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination.
预防性维护 – 按照一定的标准对设备、公用工程和厂房进行维护（计划性和非计划性的维护），该标准应能确保没有额外的污染风险。

xiii. Cleaning and disinfection.
清洁和消毒

xiv. Monitoring systems – including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination.
监测系统 – 包括引入科学合理的、能优化环境污染检测的替代方法的可行性评估。

xv. Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools.
预防机制 – 趋势分析、详细调查、明确根本原因、纠正和预防措施（CAPA）以及对全面调查工具的需求。

xvi. Continuous improvement based on information derived from the above.
基于上述信息的持续改进。

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.
CCS 应考虑到污染控制的全部方面，并进行持续和定期的回顾，酌情对药品质量体系进行更新。对现有体系的变更，应在执行前后评估其对 CCS 的任何影响。

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.
生产商应采取一切必要的步骤和预防措施保障在其设施内生产产品的无菌性。不应将无菌性或其他质量指标完全寄托在任何终端工艺或成品检测上。

3. Pharmaceutical Quality System (PQS) 制药质量体系（PQS）

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 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:

无菌产品的生产是一项复杂的活动，需要特定的控制和措施来确保所生产产品的质量。因此， 生产商的 PQS 应包括并符合无菌产品生产的特定要求，并确保所有活动得到有效控制，以便将无菌产品的微生物、微粒和内毒素/热原污染的风险降到最低。除了 GMP 指导原则（第 I 部分 –药品的基本要求）第 1 章中详述的 PQS 要求外，无菌产品生产的 PQS 还应确保：

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.
一个有效的风险管理系统被纳入产品生命周期的所有领域，目的是最大限度地减少微生物污染，确保所生产的无菌产品的质量。

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.
生产商在所生产的产品以及对产品质量有影响的设备、工程和生产方法方面有足够的知识和专业技能。

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.
对程序、工艺或设备故障进行根本原因分析，以正确识别和理解对产品的风险，从而实施适当的纠正和预防措施（CAPA）。

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.
在 CCS 的制定和维护的过程中要采用风险管理来识别、评估、降低/消除（如适用）和控制污染风险。风险管理应书面化，并应包括在降低风险和接受剩余风险方面所做决定的依据。

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.
高级管理层应对整个设施和产品生命周期的受控状态进行有效监督。风险管理结果应作为持续质量管理的一部分，在变更期间、出现重大问题、以及周期性产品质量回顾期间，定期进行回顾。

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.
与无菌产品的最终工艺步骤、储存和运输有关的过程不应损害无菌产品。应考虑的方面包括：容器的完整性、污染的风险以及通过确保产品按照注册的储存条件进行储存和维护来避免降解。

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.
负责无菌产品认证/放行的人员可以适当地获得生产和质量信息，并具备生产无菌产品和相关关键质量属性方面的足够知识和经验。这是为了使这些人能够确定无菌产品是否按照注册的质量标准和批准的工艺生产，并达到所要求的质量。

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 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.
所有不符合要求的情况，如无菌检测失败、环境监测异常或偏离于既定程序的偏差，应在认证/放行批次之前进行充分调查。调查应确定对工艺和产品质量的潜在影响，以及是否有任何其他工艺或批次受到潜在的影响。将某一产品或批次纳入调查范围或将其排除在外的理由 应予以明确说明并记录。

4. Premises 厂房

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.

无菌产品的生产应在适当的洁净室内进行，应通过作为人员气闸的更衣室和设备及物料气闸进入。洁净室和更衣室应维持在适当的洁净度标准，并提供经适当效率的过滤器过滤的送风。控制和监测应该是科学合理的，应该有效地评估洁净室、气闸和传递窗的环境条件状况。

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.

在洁净室或设施内进行部件准备、产品配制和灌装等各种操作时，应采取适当的技术和操作隔离措施，以防止混淆和污染。

4.3. Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated 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.

限制进入屏障系统（RABS）或隔离器有利于保证所需的条件，并减少人员在关键区直接干预有关的微生物污染。在 CCS 中应考虑使用它们。使用除 RABS 或隔离器以外的任何替代方法都应证明其合理性。

4.4. For the manufacture of sterile products, there are four grades of cleanroom/zone.

对于无菌产品的生产，有四个级别的洁净室/区。

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.

A 级：高风险操作的关键区域（如无菌生产线、灌装区、胶塞加料盘、敞口内包材或在初始气流保护下进行无菌连接）。通常情况下，这种条件是由局部气流保护实现的，例 如 RABS 或隔离器内的单向气流工作站。应证明和确认整个 A 级区均可维持单向气流。 应通过厂房、设备、工艺和程序设计，

尽量减少操作人员对 A 级区的直接干预（例如，没有屏障和手套箱技术的保护）。

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).
B 级：用于无菌准备和灌装，这是 A 级（当不是隔离器时）的背景洁净室。应持续监测 压差。当使用隔离器技术时，可考虑洁净度低于 B 级的洁净室（参考第 4.20 段）。

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).
C 级和 D 级：这些洁净室用于进行无菌灌装的无菌产品生产中不太关键的阶段或作为 隔离器的背景。它们也可用于终端灭菌产品的制备/灌装。(关于终端灭菌活动的具体细节 见第 8 节）。

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.
在洁净室和关键区域，所有暴露的表面应该是光滑、非渗透且无破损的，以尽量减少颗粒或微生物的脱落或积聚。

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. Sliding doors may be undesirable for this reason.
为了减少灰尘的积累并方便清洁，不应有难以有效清洁的凹槽，因此，应该使突出的窗台、架子、橱柜和设备保持在最少。门的设计应避免出现无法清洁的凹槽。由于这个原因，滑动门可能是不可取的。

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.
应筛选洁净室中使用的材料，包括房间的建造材料和房间内使用的物品，以尽量减少颗粒的产生，并在需要使用的地方允许重复使用清洁剂、消毒剂和杀孢子剂。

4.8. Ceilings should be designed and sealed to prevent contamination from the space above them.
吊顶的设计和密封应能防止来自其上方空间的污染。

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.

A 级和 B 级区内禁止设置水槽和地漏。在其他洁净室内，应在设备或水槽和地漏之间安装空气隔断装置。低级别洁净室的地漏应设计能防止倒灌的存水弯或水封，并应定期清洗、消毒和维护。

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.

设备和物料进出洁净室和关键区的转移是最大的潜在污染源之一。应评估任何有可能损害洁净室或关键区洁净度的活动，如果不能消除这些活动，应实施适当的控制。

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 –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.

应通过单向流程将物料、设备和组件传入 A 级或 B 级区。如有可能，物品应通过密封在墙 内的双端灭菌器（例如，通过双扉高压灭菌器或去热原烘箱/隧道）灭菌后进入这些区域。如果无法在传递物品时进行灭菌，则应验证并实施能够实现不引入污染的相同目标的程序，（例如，使用有效的传递消毒程序、隔离器的快速传递系统或对于气态或液态物料，使用细 菌截留性过滤器）。从 A 级和 B 级区移除物品（如物料、废弃物、环境样品）应通过单独的 单向程序进行。如果这不可能，应考虑按程序对传递（进/出物料）进行时间上的分开，并采取控制措施，以避免对进入洁净区的物品造成潜在污染。

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 rooms for entering and leaving production areas should be used. Airlocks should be designed as follows:

气闸的设计和使用应能提供物理隔离，以最大限度减少不同区域的微生物和颗粒污染，并应为在不同级别之间移动的物料和人员设置气闸。只要有可能，用于人员移动的气闸应与用于 物料移动的气闸分开。在不可行的情况下，应考虑按程序对（人员/物料）流动进行时间上 的分开。气闸应该用过滤后的空气进行有效的吹扫，以确保洁净室的级别得到保持。在"静态"状态下，最后阶段的气闸应该与它所通向的洁净室具有相同的洁净度级别（活性颗粒数 和总颗粒数）。进入和离开 B 级区时最好使用单独的更衣室。在不可行的情况下，应该考虑 按程序对（进/出）活动进行时间上的分开。如果 CCS 表明交叉污染的风险很高，则应使用单独的更衣室来进入和离开生产区。气闸的设计应遵循以下原则：

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.

人员气闸：用于人员进入的清洁度增高的区域（例如，从 D 级区到 C 级区再到 B 级区）。一般来说，洗手设施应该只在更衣室的第一阶段提供，而不应该出现在直接进 入 B 级区的更衣室里。

ii. Material airlocks: used for materials and equipment transfer.

物料气闸：用于物料和设备的传递。

- 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.

  只有被列入批准清单并在传递程序验证中评估过的物料和设备，才可以通过 气闸或传递窗进入 A 级或 B 级区。设备和物料（打算在 A 级区使用）在通 过 B 级区时应受到保护。任何需要转移的未经批准的物品都应作为例外情况 预先得到批准。应按照生产商的 CCS 应用和记录适当的风险评估和缓解措施，并应包括由质量保证部门批准的明确的消毒和监测程序。

- Pass –through hatches should be designed to protect the higher –grade environment, for example by effective flushing with an active filtered air supply.

  传递窗的设计应能保护较高等级的环境，例如通过使用主动过滤的空气进行有效风淋。

- 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.
  将物料或设备从较低级别或未分级的区域转移到较高级别的洁净区时，应进行与风险相称的清洁和消毒，并符合 CCS 的规定。

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.
进出传递窗和气闸（用于物料和人员）的门应不得同时开启。对于通向 A 级和 B 级区的气闸，应使用互锁系统。对于通向 C 级和 D 级区的气闸，至少应使用视觉和/或听觉报警系统。在需要保持区域隔离的情况下，应在互锁门的关闭和打开之间设置时间延迟。

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 should be from an area of the same or higher grade.
应向洁净室供应过滤后的空气，在所有动态条件下，相对于较低等级的背景环境，保持正压 和/或气流，并应有效地吹扫该区域。不同级别的相邻房间应该维持至少 10 帕斯卡（指导值）的压差。应特别注意对关键区域的保护。在有必要防止特定物料（如病原体、剧毒或放射性产品或活的病毒或细菌物料）蔓延时，有关送风和压力的建议可能需要修改。这种修改可能包括防止危险物料污染周围地区的正压或负压的气闸。对设施（如洁净室和供暖、通风和空 调（HVAC）系统）进行去污染，以及对离开洁净区的空气进行处理，对某些操作来说可能是必要的。当控制空气流入关键区域时，空气的来源应来自相同或更高等级的区域。

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.

洁净室/区内的气流流型应进行可视化，以证明气流没有从低等级区域进入高等级区域，空气不会来自不太干净的区域（如地板）或流经可能将污染转移到高等级区域的操作员或设备。 在需要单向气流的地方，应进行可视化研究以确定是否符合要求（参考第 4.4 和 4.19 段）。当已灌装、已封闭的产品通过一个小的出口转移到邻近的低等级洁净室时，气流可视化研究 应证明空气不会从低等级洁净室进入 B 级区域。如果空气流动被证明会对洁净区或关键区的污染风险，则应实施纠正措施，如改进设计。应在静态和动态（如模拟操作员的干预）条件下进行气流流型研究。应保留气流流型的视频记录。应记录可视化研究的结果，并在建立设施的环境监测计划时予以考虑。

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.

洁净室之间和/或隔离器与其背景之间应安装压差指示表。CCS 中应考虑设置点和压差的关键性。对确定为关键的压差应进行持续监测和记录。应建立在线报警系统，以便在空气供应出现任何故障或压差降低（低于被确定为关键压差的设定限度）时立即指示并提醒操作员。报警信号在没有评估的情况下不应该被推翻，应该有程序来概述在发出报警信号时要采取的步骤。在设置报警延迟的情况下，应该在 CCS 中对其进行评估并说明其合理性。其他压差应定期监测和记录。

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.

设施的设计应允许从 A 级和 B 级区之外观察生产活动（例如，通过准备的全面观察该区域和流程的

窗户或远程摄像头，在不进入的情况下进行观察和监督）。在设计新设施或翻修现有设施时，应考虑这一要求。

Barrier Technologies 屏障技术

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.
隔离器或 RABS（为不同的技术）以及与之相关的工艺，应被设计为通过隔离 A 级环境与周围房间的环境来提供保护。在生产过程中，应尽量减少由于物品进出所带来的危害，并由高性能的转移技术或经过验证的系统来支持，这些技术或系统能稳定地防止污染，并适合于各自的技术。

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.
所使用的技术和工艺的设计应确保在关键区保持适当的条件，以保护操作期间暴露的产品。

i. Isolators
隔离器:

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.
开放式隔离器的设计应确保在关键区域有初始气流保护的 A 级条件，在生产过程中，暴露的产品的上方和周围有单向气流吹扫。

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 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.
封闭式隔离器的设计应确保在生产过程中对暴露的产品有进行充分保护的 A 级条件。在进行简单操作的封闭式隔离器中，气流可能不完全是单向的。但是，任何紊乱的气流都不应该增加暴露产品的污染风险。在封闭式隔离器中有生 产线的情况下，应确保 A 级条件在关键区域有初始气流保护，并且在生产过程中，暴露的产品的上方和周围有单向气流吹扫。

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.
只有在有必要对产品进行抑制的情况下才可使用负压隔离器（如放射性药物产品），并应采取专门的风险控制措施，以确保关键区域不受影响。

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.
RABS 的设计应确保 A 级条件在关键区域有单向气流和初始气流保护。应维持从关键区域到支持性背景环境的正压气流。

4.20. The background environment for isolators or RABS should ensure the risk of transfer of contamination is minimized.
隔离器或 RABS 的背景环境应确保将污染转移的风险降至最低。

i. Isolators
隔离器:

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 be based on risk assessment and justified in the CCS.
开放式隔离器的背景环境一般应至少相当于 C 级，封闭式隔离器的背景应至少相当于 D 级。应基于风险评估决定背景环境的级别，并在 CCS 中说明理由。

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.
在对隔离器的 CCS 进行风险评估时，主要考虑的因素应包括（但不限于）：消毒程序、自动化程度、手套操作的影响（可能会影响关键工艺点的"初始 气流"保护）、屏障/手套完整性可能受

损的影响、使用的传递机制以及可能需要在隔离器的最终消毒前开门进行组装或维护等活动。如果发现有额外的 工艺风险，应考虑提高背景等级，除非在 CCS 中适当说明理由。

c. Airflow pattern studies should be performed at the interfaces of open isolators to demonstrate the absence of air ingress.
应在开放式隔离器的接口处进行气流流型研究，以证明没有空气进入。

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.
用于无菌生产的 RABS 的背景环境应至少达到 B 级，应进行气流模式研究，以证明在干预包括开门（如果适用）期间没有空气进入。

4.21. The materials used for glove systems (for both isolators and RABS), should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.
手套系统（包括隔离器和 RABS）所用的材料应证明具有适当的机械和化学耐受性。手套的更换频率应在 CCS 中加以规定。

i. Isolators
隔离器：

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.
对于隔离器，应使用经证明适合于任务和关键性的方法对手套系统进行检漏。应按规定的时间间隔进行检漏。一般来说，手套完整性测试应至少在每个批次或阶段性生产的开始和结束时进行。额外的手套完整性测试可能是必要的，这取决于验证的阶段性生产的长度。
手套完整性监测应包括与每次使用和在任何可能影响系统完整性的操作之后进行的目视检查。
对于生产单件或小批量产品的手工无菌加工活动，完整性确认的频率可基于其他标准，如每个

生产环节的开始和结束。

b. Integrity / leak testing of isolator systems should be performed at defined intervals.
应按规定周期进行隔离器系统的完整性/泄露测试。

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 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.
对于 RABS，在 A 级区使用的手套应在安装前进行灭菌，并在每个阶段性生产前通过验证的方法进行灭菌或有效的消毒。如果在操作过程中暴露在背景环境中，应在每次暴露后使用经批准的方法完成消毒。手套在每次使用时应进行目视检查，并应定期进行完整性测试。

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.
应适当定义和控制去污染的方法（清洁和消毒，以及，如适用，对生物物料进行灭活）。在消毒步骤之前的清洁过程是至关重要的；任何残留物都可能抑制去污染过程的有效性。还应 提供证据证明所使用的清洁剂和消毒剂不会对 RABS 或隔离器内生产的产品产生不利影响。

i. For isolators
对于隔离器

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 used (cleaning and sporicidal bio –decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.
隔离器内部的消毒过程应该是自动化的，经过验证并控制在规定的参数范围内，并且应该包括适当形式的杀孢子剂（如气态或蒸汽形式）。手套应适当展开，手指分开，以确保与药剂的接触。所使用的方法（清洁和杀孢子剂消毒）应使隔离器的内表面和关键区域没有活的微生物。

ii. For RABS
对于 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.
杀孢子消毒应包括一种杀孢子剂的日常应用，该方法已被验证并证明能够稳定有效地涵盖内表面的所有区域，并确保有适合无菌加工的环境。

Cleanroom and clean air equipment qualification 洁净室和空气净化设备确认

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.
用于无菌产品生产的洁净室和洁净空气设备，如单向气流装置(UDAF)、RABS 和隔离器，应根据所需的环境特征进行确认。每个生产操作都需要有在动态条件下的适当的环境清洁度等级，以尽量减少被处理的产品或物料的污染风险。在"静态"和"动态"条件下，应该保持适当的清洁度等级。

4.24. Cleanrooms and clean air equipment should be qualified using methodology in accordance with the requirements of Annex 15. Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring.
洁净室和洁净空气设备应采用符合附录 15 要求的方法进行确认。洁净室确认（包括分级）应与动态环境监测明确区分开来。

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):
洁净室和洁净空气设备的确认是评估已分级洁净室或洁净空气设备与其预期用途的符合程度的总体过程。作为附件 15 的确认要求的一部分，洁净室和洁净空气设备的确认应包括（在与安装的设计/操作有关的情况下）：

i. Installed filter system leakage and integrity testing
已安装过滤系统检漏和完整性测试

ii. Airflow tests – volume and velocity.
气流检测 –风量和流速

iii. Air pressure difference test.
压差检测

iv. Airflow direction test and visualisation.
气流流向检测和可视化

v. Microbial airborne and surface contamination.
浮游菌和表面污染

vi. Temperature measurement test.
温度监测测试

vii. Relative humidity test.
相对湿度测试

viii. Recovery test.
自净测试

ix. Containment leak test.
气密泄漏测试

Reference for the qualification of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards.
洁净室和洁净空气设备的确认参考可以在 ISO 14644 系列标准中找到。

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 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).
洁净室分级是洁净室确认的一部分，是通过测量总颗粒浓度，按洁净室或洁净空气设备的标准来评估空气洁净度水平的方法。分级活动的安排和执行，应避免对工艺或产品质量造成任何影响。例如，首次分级应该在模拟操作过程中进行，重新分级应该在模拟操作过程或无菌工艺模拟（APS）过程进行。

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.

对于洁净室的分级，应该测量大于等于 0.5 和 5 微米的颗粒的总数。这种测量应按表 1 中规定的限度，在静态和模拟操作中进行。

Table 1: Maximum permitted total particle concentration for classification

表 1：分级中允许的最大总粒子浓度

Grade 级别	Maximum limits for particle 最大粒子限度 ≥ 0.5 μm/m³		Maximum limits for particle 最大粒子限度 ≥ 5 μm/m³	
	At rest 静态	In operation 动态	at rest 静态	In operation 动态
A	3 520	3 520	Not specified[a] 未规定	Not specified[a] 未规定
B	3 520	352 000	Not specified[a] 未规定	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined[b] 非事先规定(b)	29 300	Not predetermined[b] 非事先规定(b)

(a) Classification including 5μm particles may be considered where indicated by the CCS or historical trends.

在 CCS 或历史趋势中有显示的情况下，应该考虑包括 5μm 颗粒的分级。

(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.

对于 D 级，没有预定的动态限度。如适用，生产商应根据风险评估和日常数据来确定动态限度。

4.28. For classification of the cleanroom, the minimum 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.

对于洁净室的分级，取样位置的最低数量及其定位可在 ISO 14644 第 1 部分中找到。对于无菌生产

区和背景环境（分别为 A 级区和 B 级区），应考虑增加额外的取样位置，并对所有的关键生产区，如灌装点和包材的加料盘进行评估。关键生产区应通过书面的风险评估和对该区域内要进行的工艺和操作的了解来确定。

4.29. Cleanroom classification should be carried out in the “at rest” and “in operation” states.
洁净区分级应该分别在“静态”和“动态”下进行。

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.
“静态”的定义是：所有公用设施的安装都已完成，包括任何功能性 HVAC 系统，主要生产设备按规定安装，但没有运行，房间内没有人员在场。

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 operational work.
“动态”的定义是：洁净室安装完毕，HVAC 系统完全运行，设备安装完毕并在生产商规定的运行模式下运行，最大人数在场进行或模拟日常运行工作的状态。

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.
应在操作和清场/清洁活动完成后的"自净"阶段内实现上表 1 中给出的“静态”下的总颗粒限度。"自净"时间（指导值小于 20 分钟）应在房间的确认过程中确定，在程序中书面化并遵守，以便在操作过程中当洁净度受到破坏时，使其恢复到合格状态。

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 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.
单向气流系统的送风速度应在确认方案中明确说明其合理性，包括风速测量的位置。风速的 设计、

测量和维持应确保有适当的单向气流在工作位置（如：进行高风险操作、产品和/或包装组件暴露的地方）为产品和敞开的包装组件提供保护。单向气流系统应在工作位置提供 0.36 –0.54 米/秒（指导值）范围内的均匀风速，除非 CCS 中有其他的科学合理性论证。气流可视化研究应与风速测量相关联。

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.

洁净室微生物污染水平应作为洁净室确认的一部分。取样点的数量应基于书面的风险评估和从房间分级、气流可视化研究中获得的结果以及对该区域将进行的工艺和操作的了解。表 2 中给出了每个等级在确认期间的微生物污染的最大限度。确认应包括静态和动态。

Table 2: Maximum permitted microbial contamination level during qualification
表 2：确认阶段允许的最大微生物污染水平

Grade 级别	Air sample cfu/m³ 浮游菌 cfu/m³	Settle plates (diameter 90 mm) cfu/4 hours [a] 沉降菌（直径90mm）cfu/4小时[a]	Contact plates (diameter 55 mm) cfu/plate 表面微生物（直径55mm）cfu/皿
A[b]	No growth [b] 没有生长		
B	10	5	5
C	100	50	25
D	200	100	50

[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.

沉降碟应在操作过程中暴露，并在最多 4 小时后根据需要更换。暴露时间应该基于回收率研究，不应使所用的培养基干燥。

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 tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.

注 1：表中为特定等级指定的所有方法都应用于该特定等级区域的确认。如果不使用表中的某种方法，或使用其他方法，应适当说明所采取的方法的合理性。

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.
注 2：本文件中使用了 CFU 的限度。如果使用不同的或新的技术，其呈现的结果与 CFU 不同，生产商应科学地说明所用限度的合理性，并在可能的情况下将其与 CFU 关联起来。

Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply.
注 3：对于人员更衣确认，应采用表 6 中给出的接触碟和手套印迹的限度。

Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.
注 4：采样方法不应引起对生产操作造成污染的风险。

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:
洁净室与洁净空气设备的再确认应该根据规定的程序定期执行，洁净室区域再确认至少应报告以下内容：

- Cleanroom classification (total particle concentration).
  洁净室分级（总颗粒浓度）

- Integrity test of final filters.
  终端过滤器的完整性

- Airflow volume measurement.
  气流流量的测量

- Verification of air pressure difference between rooms.
  不同房间之间的压差确认

- 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).
  风速测试（注：对于 B 级、C 级和 D 级，风速测试应根据作为 CCS 一部分的书面风险评估来进行。但是，对于有单向气流送风的灌装区（例如，当灌装最终灭菌的产品或 A 级和 RABS 的背

景），需要进行测试。对于具有非单向气流的等级，应以自净测试来代替风速测试)。

The maximum time interval for requalification of grade A & B areas, is 6 months.
A 级和 B 级区再确认的最长时间间隔为 6 个月。

The maximum time interval for requalification of grade C & D areas, is 12 months.
C 级和 D 级区再确认的最长时间间隔为 12 个月。

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 change management process. Examples of changes to be considered include but are not limited to the following:
在为纠正设备或设施的缺陷而采取的整改措施完成后，或在设备、设施或工艺发生变更之后，也应进行至少包括上述测试的适当再确认。应通过变更管理程序来确定变更的重要性。需要考虑的变更案例包括但不限于以下内容：

i. Interruption of air movement which affects the operation of the installation.
空气流动的中断，影响了装置的运行。

ii. Change in the design of the cleanroom or of the operational setting parameters of the HVAC system.
洁净室设计或 HVAC 系统运行设置参数的变更。

iii. Special maintenance which affects the operation of the installation (e.g. change of final filters).
影响装置运行的特殊维护（例如，更换最终过滤器）。

Disinfection 消毒

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 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).

洁净室的消毒尤其重要。应该按照书面程序对它们进行彻底的清洁和消毒。为使消毒工作有效，应事先进行清洁以清除表面污染。清洁程序应能有效去除消毒剂残留。应采用一种以上的消毒剂，以确保当它们具有不同的作用机制时，它们的联合使用对细菌和真菌都有效。应定期使用杀孢子剂消毒。应定期进行监测，以评估消毒程序的有效性，并检测微生物菌群类型的变化（如对目前使用的消毒制度有抵抗力的生物）。

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.
消毒过程应进行验证。验证研究应证明消毒剂在特定的使用方式和在表面材料类型上，或者（如果有适当理由）代表性的材料上的适用性和有效性，并应支持所配制的溶液的在用有效期。

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 appropriate vendor qualification.
在 A 级和 B 级区使用的消毒剂和清洁剂在使用前应该是无菌的。在 CCS 中有规定时，C 级 和 D 级区使用的消毒剂也可能要求是无菌的。如果消毒剂和清洁剂是由无菌产品生产商稀 释/配制的，则应以防止污染的方式进行，并应监测其是否受到微生物污染。稀释液应保存在事先清洁过的容器中（如有必要，应进行灭菌），并应只在规定的时间内保存。如果消毒剂和洗涤剂是"现成的"，那么在成功完成适当的供应商资格确认后，可以接受 CoA 或合格证上的结果。

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.
在对洁净室和相关表面进行熏蒸或蒸汽消毒（如气相过氧化氢）时，应获知并验证任何熏蒸剂和分散系统的有效性。

5. Equipment 设备

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.
应有书面的、详细的设备设计说明（包括适当的工艺和仪表图）。这应构成初始确认文件包的一部分，并保持更新。

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).
设备监测要求应在开发的早期阶段在"用户需求标准"中定义，并在设备确认期间进行确认。应确认工艺和设备报警事件，并对其趋势进行评估。评估警报的频率应基于其关键性（关键性警报应立即审核）。

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.
在可行的情况下，设备、配件和服务的设计和安装应使操作、维护和修理可在洁净室外进行。如果维修必须在洁净室内进行，而不能保持所要求的洁净度和/或无菌标准，那么应考虑采取预防措施，如限制特定人员进入工作区，制定明确的工作方案和维修程序。还应考虑额外的清洁、消毒和环境监测。如果需要对设备进行灭菌，应尽可能在完全重新组装后进行。

5.4. The cleaning process should be validated to be able to:
清洁程序应进行验证，以使其能够：

i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.
清除任何会对所用消毒剂的效果产生不利影响的残留物或碎屑。

ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.
在加工过程中和消毒前，尽量减少产品的化学、微生物和微粒污染。

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).
对于无菌工艺，直接和间接与产品接触的部件都应进行灭菌。直接接触产品的部件是指产品经过的部件，如灌装针头或泵。间接接触产品的部件是不接触产品的设备部件，但可能与其他已灭菌的表面接触，其无菌性对整个产品的无菌性至关重要（例如，已灭菌的物品，如胶塞加料盘和导轨，以及已灭菌的包装组件）。

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 completion of maintenance, their return to use should be approved.
所有设备，如灭菌柜、空气处理系统（包括空气过滤）和水系统，都应进行确认、监测和计划性维护。在维护完成后，应批准后才能恢复使用。

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.
如果要对产品无菌性至关重要的设备进行计划外维修，应评估对产品无菌性的潜在影响并记录。

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).
传送带不应通过 A 级或 B 级区与空气清洁度较低的加工区之间的隔断，除非传送带本身被持续消毒（例如，在灭菌隧道烘箱中）。

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.
应对粒子计数器（包括采样管）进行确认。应考虑生产商推荐的管子直径和弯曲半径的标准。除非有正当理由，否则管子的长度通常不应超过 1 米，并且应尽量减少弯曲数量。应将带有较短采样管的便携式粒子计数器用于房间分级。应在单向气流系统中使用等动力学采样头。它们应具有适当的朝向，并尽可能地靠近关键位置，以确保样品的代表性。

6. Utilities 公用系统

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.
适用于公用系统的控制的性质和程度应与公用系统相关的产品质量风险相称。这种影响应通过风险评估来确定，并作为 CCS 的一部分进行记录。

6.2. In general, higher risk utilities are those that:
通常情况下，风险较高的公用系统如下：

i. Directly contact product e.g. water for washing and rinsing, gases and steam for sterilisation.
直接接触产品，比如清洗和冲洗用水，灭菌用的气体和蒸汽。

ii. Contact materials that will ultimately become part of the product.
接触最终将成为产品一部分的物料。

iii. Contact surfaces that come into contact with the product.
与产品接触的接触面。

iv. Otherwise directly impact the product.
通过其他方式直接影响产品。

6.3. Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected.
公用系统的设计、安装、确认、运行、维护和监测方式应确保公用系统的功能符合预期。

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.
对高风险公用系统的关键参数和关键质量属性的结果应定期进行趋势分析，以确保系统的性能保持合适。

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:
公用系统的安装记录应在系统的整个生命周期内保持。这种记录应包括当前的图纸和原理图，建造材料清单和系统质量标准。通常情况下，重要的信息包括以下属性：

i. Pipeline flow direction, slopes, diameter and length.

管道流向、坡度、直径和长度。

ii. Tank and vessel details.
罐与釜的详情。

iii. Valves, filters, drains, sampling and user points.
阀门、过滤器、排水、取样和使用点。

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.
洁净室中不应该有管道、通风设施和其他公用设施。如果不可避免，那么它们的安装应避免造成凹槽、未密封的开口和难以清洁的表面。安装方式应便于对管道的外表面进行清洁和消毒。

Water systems 水系统

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.
水制备系统和分配系统的设计、建造、安装、调试、确认、监测和维护应防止微生物污染，并确保有合适质量的可靠水源。应采取措施最大限度地减少颗粒物、微生物污染/增殖和内毒素/热原存在的风险（例如，管道适当倾斜以保证完全排空及避免死角）。如果系统中有过滤器，应特别注意对其进行监测和维护。生产的水应符合相关药典的现行专论。

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.
水系统应该是经过确认和验证的，以保持适当的物理、化学和微生物控制水平，应同时考虑到季节性变化的影响。

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.
水流在分配系统的管道中应保持湍流状态，以最大程度降低微生物粘附和后期形成生物膜的风险。应在确认期间确定流速，并进行日常监测。

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 reverse osmosis coupled with other appropriate techniques such as electrodeionization (EDI), ultrafiltration or nanofiltration.

注射用水(WFI)应该用符合确认过程中定义的质量标准的水生产，其储存和分配方式应尽量减少微生物生长的风险(例如在 70℃以上的温度下持续循环)。WFI 应通过蒸馏或相当于蒸馏的纯化过程来生产。这可能包括反渗透加上其他适当的技术，如电去离子（EDI）、超滤或纳滤。

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).

如果 WFI 储罐配备了疏水性细菌截留呼吸器，则过滤器不应成为污染源，并在安装前和使用后测试过滤器的完整性。应采取控制措施，防止在过滤器上形成冷凝水（例如，通过加热）。

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.

为了最大限度降低生物膜形成的风险，应按照预先确定的时间表进行水系统的灭菌、消毒或 再生，并作为超标结果后的补救措施。用化学品对水系统消毒后，应执行经过验证的淋洗/ 冲洗程序。消毒/再生后应进行水质检测。在水系统恢复使用前，化学检测结果应得到批准，在认证/放行用该系统的水生产的批次得到批准前，微生物/内毒素结果应确认符合质量标准。

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 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.

应定期对水系统进行持续的化学和微生物监测，以确保水继续符合药典的预期。警戒限应基于最初的确认数据制定，此后根据随后的再确认、常规监测和调查中获得的数据定期进行重新评估。应当对持续的监测数据进行回顾，以确定系统性能的任何不良趋势。取样程序应反映 CCS 的要求，并应包括所有出口和使用点，以规定的时间间隔，确保定期获得有代表性的水样进行分析。取样计划应以确认数据为基础，应考虑潜在的最差条件取样位置，并应确保在生产用水过程中的每一天至少包括一个有代表性的样本。

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.

应对超警戒限的异常情况进行记录和审核，并对其进行调查以确定该超标是否为个案（孤立事件），或者结果是否显示出不良趋势或系统恶化。应对每个超出行动限的异常情况进行调查，以确定可能的根本原因以及工艺用水对产品质量和生产工艺的任何潜在影响。

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.

注射用水系统应包含连续监测系统，例如总有机碳（TOC）和电导率，因为这样会比非连续取样能够更好地反应系统的整体性能。传感器的位置应基于风险。

Steam used as a direct sterilising agent 用于直接灭菌的蒸汽

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.

纯蒸汽（洁净蒸汽）发生器的供水应进行适当纯化。纯蒸汽发生器的设计、确认及运行应确保蒸汽质量符合规定的化学和内毒素水平。

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.

用作直接灭菌的蒸汽应具有适当的质量，且不应含有可能引起产品或设备污染的水平的添加剂。对于提供用于物料或产品接触表面（如蒸汽灭菌柜的多孔硬物装载模式）直接灭菌用蒸汽的发生器，蒸汽冷凝水应符合相关现行药典的 WFI 专论要求（蒸汽冷凝水不强制要求检测微生物）。应制定适当的取样计划，以确保定期对获得的代表性的纯蒸汽进行分析。灭菌用纯蒸汽质量的其他方面应根据验证过的参数定期进行评估。这些参数应包括（除非另有正当理由）：不凝性气体、干度值（干度分数）和过热值。

Gases and vacuum systems 气体和真空系统

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 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.

与产品/内包装容器表面直接接触的气体应具有适当的化学、粒子和微生物质量。所有相关参数，包括油分和水分，应当进行规定，同时考虑气体的使用和类型，气体发生系统的设计，应符合相应药典当前专论或产品质量要求（如适用）。

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.

用于无菌工艺的气体应在使用点用除菌过滤器（最大标示孔径为 0.22µm）过滤。如果过滤器每批都要使用（如过滤用于无菌灌装产品的保护气体）或用作产品储罐的呼吸器，则过滤器 应当进行完整性测试，且测试结果应作为产品批次认证/放行的一部分进行审核。任何位于最终除菌滤器后的传输管道或软管都应当进行灭菌。当工艺过程中用到气体时，应在使用点定期对气体进行微生物监测。

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.

当真空或压力系统的回流对产品构成潜在风险时，应当具有防止在真空或压力系统关闭时回流的机制。

Heating and cooling and hydraulic systems 加热、冷却和液压系统

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 appropriate controls to contain any spillage and/or cross contamination associated with the system fluids.
与液压、加热和冷却系统相关的设备的主要部分应尽可能的放在灌装室外。应该采取适当的 措施来控制与各系统液体有关的任何泄漏和/或交叉污染。

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).
这些系统的任何泄漏，在对产品构成风险时，都应当都可被检测（例如，泄漏指示系统）。

7. Personnel 人员

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.
生产厂家应确保具有足够的合适人员，这些人员应经过适当的资质确认，在无菌产品生产、检验以及任何用于该工厂生产操作的具体生产技术方面经过培训并具有经验，以便确保符合有关无菌产品生产和处理的 GMP 要求。

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.
洁净室中应只有最少数量的所需人员在场。应该在首次确认和无菌工艺模拟等活动中确定、记录并考虑洁净区内操作人员的最大数量，以确保不会破坏无菌保证。

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 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.
执行清洁、维护保养、监测及其他进入洁净区的所有人员均应接受定期培训、更衣确认以及关于无菌产品正确生产训导的评估。该培训应包括关于微生物和卫生的基础知识，特别关注洁净室行为、污染控制、无菌技术、无菌产品的保护（针对进入 B 级洁净室和/或对 A 级进行干预的操作员工）以及产品非无菌对患者产生的潜在安全影响。培训水平应基于人员职能和工作区域的关键程度。

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.
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。应通过评估及至少每年定期再评估确认是否符合无菌更衣程序，并应包括目视和微生物评估（使用，如戴手套的手指、前臂、胸部和头罩

（口罩/前额）等监测位置）。预期限度请参阅 9.30 节）。仅限于经过资质确认，即通过更衣评估并参与过成功 APS 的人员可无人监督地进入正在或将要进行无菌操作的 A 级和 B 级区域。

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.

未经资质确认的人员不得进入处于动态的 B 级洁净区和 A 级区。在特殊情况下，如果这些人员需要进入，生产厂家则应该建立书面程序来规定未经资质确认的人员进入 A 级和 B 级区的流程。生厂厂家的经授权人员应该指导未经资质确认人员的活动，并评估这些活动对该区域洁净度的影响。这些人员的进出应按照 PQS 进行评估和记录。

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 APS.

应建立关于取消人员在洁净室工作或无人监督进入洁净室资格的制度，其基于持续评估和/或人员监测计划不良趋势的识别和/或由于参与失败的 APS。一旦被取消资格，在允许该操作员参与任何无菌操作之前，应完成再培训和资格再确认。对于进入 B 级洁净室 或对 A 级进行干预的操作员，资格再确认应包括参与一次成功的 APS。

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.

高标准的人员卫生和清洁对于防止过多散发脱落物或增加引入微生物污染的风险至关重要。应指示参与无菌产品生产的人员报告任何可能导致散发异常数量或类型污染物的任何健康状况或疾病，并因此不得进入洁净区。应由指定的合格人员提供那些可能引入过多微生物危害的人员的健康状况和采取的措施，并在程序中加以规定。

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.

从事当前生产工艺中未使用到的人体或动物组织材料或者微生物培养物加工处理的人员，或从事任何可能对质量产生负面影响活动（例如微生物污染）的人员，不得进入洁净区。除非遵循了明确定义的、有效去出污染和进入的程序，并进行了记录。

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 grade in which they are used. The use and disinfection of such equipment should be included in the CCS.

手表、化妆品、珠宝首饰、移动电话等个人物品和任何其他非必需物品不得带入洁净区。洁净室中使用的电子设备，例如生产厂家提供的仅用于洁净室的移动电话和平板电脑，如果设计得当，并可以进行与其使用的级别相称的清洁和消毒，则可能被接受。此类设备的使用和消毒应包含在 CCS 中。

7.10. 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.

洁净区更衣和洗手应按照书面程序执行，该程序旨在能最大程度渐少洁净区的工作服污染和/或污染物转移到洁净区。

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 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.

洁净服及其质量应与工艺和工作区域的级别相适应。洁净服的穿着方式应能保护产品免受污染。 当所选择的服装类型需要为操作员提供针对产品的保护时，不应损害产品免受污染的保护。 在更衣前

后，应立即目视检查洁净服的清洁度和完整性。退出洁净室时还应检查洁净服的完整性。 对于已灭菌的洁净服和眼罩，应特别注意确保已对它们进行灭菌处理，且在规定的保存时间内， 并在使用前对包装进行目视检查以确保其完整性。如果发现可重复使用的洁净服（包括眼罩）损坏或达到经确认研究设定的更换频次时应更换。洁净服的确认应考虑任何必要的洁净服检测要求，包括单凭目视检查无法识别的损坏。

7.12. Clothing should be chosen to limit shedding due to operators' movement.
应选择洁净服用以限制由于操作员的移动而散发的脱落物。

7.13. A description of typical clothing required for each cleanliness grade is given below:
各洁净级别典型着装要求的说明如下:

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 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 级（包括进入/干预 A 级）：在更衣前应穿上专用于无菌服内的适当服装（见 7.14 节）。穿上已灭菌洁净服时，应戴上经过适当灭菌、无颗粒物的橡胶或塑料手套。无菌头罩应包住所有毛发（包括面部毛发），当其与洁净服其余部分分开时，应将头罩塞入无菌服的领口内。 应当佩戴无菌口罩和无菌眼罩（如护目镜），以覆盖并包裹所有的面部皮肤，防止散发飞沫和颗粒。应穿上经灭菌的鞋子（如，高筒套靴）。裤腿应当塞进套靴内。洁净服的袖子应塞进第二副无菌手套中，第二副手套戴在穿洁净服时戴的那副手套外面。防护服应尽 量减少纤维或颗粒的脱落，并能滞留身体脱落的颗粒。应在洁净服确认期间对洁净服的颗粒脱落和颗粒滞留效率进行评估。洁净服的包装和折叠方式应使操作员在更衣时能够不接触到洁净服的外表面，并防止洁净服接触地板。

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.

C 级：应遮盖住头发和胡须。应穿着手腕处收紧的高领连体或上下两件式长裤套装，并应穿适当消毒的鞋子或鞋套。它们应能尽量减少纤维和微粒的脱落。

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.
D 级洁净区：应遮盖住头发和胡须。应穿着普通防护服和经过适当消毒鞋子或鞋套。 应当采取适当措施，以避免将外部污染物带入洁净区。

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.
当执行 CCS 规定的被认为具有污染风险的活动时，在 C 级和 D 级区可能需要额外的防护服包括手套和口罩。

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 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.
洁净室更衣应在适当清洁级别的更衣室内进行，以确保保持洁净服的清洁度。不得将包括 袜子在内的户外衣物（个人内衣除外）带入直接通往 B 级和 C 级区的更衣室。在进入 B 级和 C 级的更衣室之前，应穿着覆盖整个手臂和腿部的连体或上下两件式工作长裤套装，以及覆盖脚部的工作袜。工作服和袜子不应对更衣区域或工艺产生污染风险。

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.
进入 B 级或 A 级区域的每个操作员都应在每次进入时穿上合适尺寸的洁净、灭菌的防护服（包括眼罩和口罩）。在一个班次内灭菌洁净服更换前可以穿着的最长时间应作为洁净服确认的一部分。

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.
操作过程中应定期对手套进行消毒。如果洁净服和手套受损或对产品有任何污染风险时，则应立即更换。

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.
可重复使用的洁净服应在与生产操作充分隔离的洗衣设施中清洗，使用经过确认的程序以确保洁净服在重复洗涤过程中不会损坏和/或被纤维或颗粒污染。使用的洗衣设施不应引入污染或交叉污染的风险。洁净服处理和使用不当会损坏纤维并增加颗粒脱落的风险。洗涤后和包装前，应目视检查洁净服是否损坏和清洁度。洁净服管理程序应作为洁净服确认计划的一部分进行评估和确定，且洁净服管理程序应包括洗衣和灭菌循环的最大次数。

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.
在洁净区中，对生产过程不重要的活动应保持在最低限度，尤其是在进行无菌操作时。人员的移动应缓慢、受控且有条不紊，以避免由于剧烈活动而导致颗粒和微生物的过多发散。 进行无菌操作的操作人员应始终遵循无菌技术，以防止气流变化可能将质量较低的空气引入关键区域。应限制关键区附近的活动，并应避免阻碍单向气流（首过空气）。气流可视化研究的回顾应被视为培训计划的一部分。

8. Production and Specific Technologies 生产与专项技术

Terminally sterilised products 最终灭菌产品

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.
组分和物料的配制应至少在 D 级环境下进行，以减少微生物、内毒素/热原和微粒污染的风险，以使得产品适于灭菌。如产品有很高或异常的微生物污染风险（如，容易长菌的产品和 /或在灌装前需要等待很长时间和/或未在密闭罐内进行加工的），其配制应至少在 C 级环境 下进行。在最终灭菌之前，软膏，霜剂，混悬剂和乳剂制备应在 C 级环境中进行。关于最 终灭菌兽药产品的具体指导见 GMP 指南附件 4。

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.
内包装容器和组件应当使用经验证的程序进行清洗，以确保微粒、内毒素/热原和生物负载污染被适当地控制。

8.3. Filling of products for terminal sterilisation should be carried out in at least a grade C environment.
用于最终灭菌的产品，其灌装应当至少在 C 级环境下进行。

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.
当 CCS 中指明产品存在异常的环境污染风险，例如灌装操作缓慢，容器口较宽或需要在密封前暴露数秒，则产品灌装需至少在 C 级背景下的 A 级环境进行。

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.
在可能的情况下，药液的生产工艺应包含使用微生物截留过滤器的过滤步骤，以降低在灌装至最终产品容器前生物负载水平和微粒，而且应规定配制后至灌装前最大允许时间。

8.6. Examples of operations to be carried out in the various grades are given in Table 3.
表 3 列举了各级洁净区内生产操作示例。

Table 3: Examples of operations and grades for terminally sterilised preparation and processing operations
表 3：最终灭菌制剂和加工操作对应的操作和洁净级别举例

Grade A	- Filling of products, when unusually at risk. 存在异常风险时，产品灌装。
Grade C	- Preparation of solutions, when unusually at risk. 存在异常风险时，溶液配制。 - Filling of products. 产品灌装。
Grade D	- Preparation of solutions and components for subsequent filling. 为后续灌装配制溶液和组分。

Aseptic preparation and processing 无菌准备和处理

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.
无菌工艺应被清晰定义。无菌工艺的相关风险及任何相关要求，都应被识别、评估和适当地控制。工厂污染控制策略应明确规定上述控制的可接受标准、监控要求及有效性审核。应描述并实施用于控制上述风险的方法和程序。接受的其他风险应形成正式文件。

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 materials liable to generate particles and fibres should be minimized in cleanrooms.
在无菌环境的准备阶段，在所有工序（包括散装产品灭菌前后的阶段），直至产品密封于最终容器中，应根据工厂污染控制策略，采取预防措施以最大程度地降低微生物、内毒素/热原和微粒污染。洁净室内应尽量减少使用易产生微粒和纤维的材料。

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).
如可能，应考虑采用 RABS、隔离器或其它系统，以减少对 A 级区的关键干预并尽可能降低污染风险。可考虑采用机器人和工艺自动化以消除直接的人员关键干预（如，干热隧道，自动装载冻干机，SIP）。

8.10. Examples of operations to be carried out in the various environmental grades are given in Table 4.
在不同级别环境下进行的操作举例见表 4。

Table 4: Examples of operations and grades for aseptic preparation and processing operations
表 4：无菌准备和加工操作对应的操作和洁净级别的举例

Grade A	- Aseptic assembly of filling equipment. 灌装设备的无菌装配 。 - Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilising grade filter. These connections should be sterilised by steam –in –place whenever possible. 最终除菌过滤器之后在无菌条件下(已灭菌产品的接触表面暴露处)进行的连接。这些连接应尽可能采用 SIP 进行灭菌。 - Aseptic compounding and mixing. 无菌配液和混合。 - Replenishment of sterile bulk product, containers and closures. 无菌待分装/灌装产品、容器和封盖的补充。 - Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. 移除和冷却灭菌柜中未受保护（如，没有包装）物品。 - Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. 无菌灌装线中未包裹的无菌内包装组件的暂存和传送。 - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. 无菌灌装，容器（如安瓿瓶）的封口，西林瓶的密封，开口或是半压塞西林瓶的转移。 - Loading of a lyophilizer. 冻干机的装载。

Grade B	- Background support for grade A (when not in an isolator). 支持 A 级区（当不在隔离器中）的背景区域。 - Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A. 在保护其免受周围环境影响的情况下，转运设备、部件和附属物品，以将 其引入 A 级区。
Grade C	- Preparation of solutions to be filtered including sampling and dispensing weighing. 待过滤溶液的配制，包括取样和配料称量。
Grade D	- Cleaning of equipment. 设备清洁。 - Handling of components, equipment and accessories after cleaning. 组件，设备和附件清洁后的处理。 - Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation. 灭菌前在 HEPA 过滤后的气流下组装已清洁的组件、设备。 - Assembly of closed and sterilised SUS using intrinsic sterile connection devices. 使用固有无菌连接设备进行密闭已灭菌的 SUS 的装配。

8.11. For sterile products where the final formulation cannot be filtered, the following should be considered:
对于最终配方不能过滤的无菌产品，应考虑以下几点：

i. All product and component contact equipment should be sterilised prior to use.
所有与产品和组分接触的设备在使用前应灭菌。

ii. All raw materials or intermediates should be sterilised and aseptically added.
所有原料或中间产品均应经过灭菌，并且以无菌操作方式添加。

iii. Bulk solutions or intermediates should be sterilised.
分装/灌装前的料液或中间产品应经过灭菌。

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.
与产品直接接触或间接接触的已灭菌设备、组件和附属品的拆包、组装应视为无菌过程并在 B 级背景的 A 级下操作，以及无菌产品的设备组装和灌装应视为无菌过程，并在 B 级背景下 的 A 级区进行。当使用隔离器时，背景区域应符合 4.20 的要求。

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.

当产品和组件暴露在环境并且产品不会随后过滤(通过除菌级别过滤)或最终灭菌时，无菌产品如软膏、乳膏、悬浮液和乳剂的制备和罐装应该在 B 级背景下的 A 级区域进行。当使用 隔离器或 RABS 时，背景区域应符合 4.20。

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.

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.

无菌连接应在 B 级背景下的 A 级进行，除非后续有在线灭菌处理，或使用验证过的固有无菌连接设备进行连接以尽可能减少任何周围环境中的潜在污染。固有无菌连接设备的设计应降低污染风险。

无菌连接应在 B 级背景下的 A 级进行，除非后续有在线灭菌处理，或使用验证过的固有无菌连接设备进行连接以尽可能减少任何周围环境中的潜在污染。固有无菌连接设备的设计应降低污染风险。当使用隔离器时，背景区域应符合 4.20。无菌连接应进行适当评估并确认其有效性。固有无菌连接设备的要求参见 8.129 和 8.130。

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.

应该采用工程设计方案，如预装和已灭菌的设备，来尽量减少无菌操作（包括非内部无菌连接设备）。如可行，接触产品的管道和设备应预装，并进行在线灭菌。

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 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.

应具备经过批准和确认的可进行干预活动的清单，包括可能发生在生产过程中的固有的和纠正性的干预（参见第 9.34 段）。应仔细设计干预措施，以确保有效降低环境、过程和产品污染的风险。设计干预措施的过程应包括考虑对气流和关键表面和产品的任何影响。应尽可能使用工程解决方案，以尽量减少操作员在干预期间的侵入。应始终遵守无菌技术，包括适当使用无菌工具进行操作。列出固有干预和纠正干预类型以及如何执行它们的程序应首先 通过风险管理和 APS 进行评估，并保持更新。只有在特殊情况下才能使用未经确认的干预措施，并适当考虑与干预措施相关的风险并获得质量部门的批准。所进行干预的细节应根据 制造商的 PQS 进行风险评估、记录和全面调查。任何未经确认的干预措施都应由质量部门进行彻底评估，并在批次处置期间予以考虑。

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).

干预和停止应记录在批记录中。 每个生产线停止或干预都应在批次记录中充分记录，包括相关的时间、事件持续时间和所涉及的操作员（参见第 9.34 段）。

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:

无菌制备和处理的各环节的持续时间应尽可能减少，应限定在规定的和经过验证的最长时间内，包括：

i. The holding time between equipment, component, and container cleaning, drying and sterilisation.
设备，组件和容器的清洁、干燥及灭菌的之间保持时长。

ii. The holding time for sterilised equipment, components, and containers before use and during filling/assembly.
设备、部件和容器灭菌后至使用前，以及组装/灌装期间的保持时间。

iii. The holding time for a decontaminated environment, such as the RABS or isolator before use.
已净化环境如 RABS 或隔离器，在使用之前的保持时间。

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.
产品配制开始到灭菌或使用微生物截留过滤器（如果适用）过滤的时间，以及到最终无菌灌装工序结束之间的时间。基于产品的成分和规定的储存方法，每个产品应有最长的允许保持时间。

v. The holding time for sterilised product prior to filling.
已灭菌产品灌装前的保持时间。

vi. The aseptic processing time.
无菌工艺时间。

vii. The filling time.
灌装时间。

8.19. Aseptic operations (including APS) should be observed on a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations including operator behaviour in the cleanroom and address inappropriate practices if detected.
无菌操作(包括 APS)应由具有无菌工艺专业知识的人员定期观察，以确认操作的正确性，包括操作员在洁净室中的行为,并在发现不当操作时予以纠正。

Finishing of sterile products　无菌产品最终处理

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).
敞口内包装容器应保持在具有第 4.20 段所述技术背景的 A 级条件下。对于部分加塞的小瓶或预灌装注射器（请参阅第 8.126 段）

8.21. Final containers should be closed by appropriately validated methods.
最终容器应通过适当经验证的方法密封。

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 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.

通过熔封进行最终容器密封，例如吹灌封 (BFS)、制灌封 (FFS)、小容量和大容量注射剂 (SVP & LVP) 袋、玻璃或塑料安瓿，应评估、确定影响密封完整性的关键参数和变量，在操作过程中得到有效控制和监控。 玻璃安瓿瓶、BFS 装置和小容量容器（≤100 ml）应使用经过验证的方法进行 100% 完整性测试。 对于通过熔合封闭的大容量容器（>100 毫升），在科学合理的情况下，根据证明现有工艺的一致性和高水平的工艺控制的数据，减少取样是可以接受的。 应该注意的是，目视检查不被视为可接受的完整性测试方法。

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.

应采集使用非融合系统的产品样品，并使用经过验证的方法检查其完整性。测试频率应基于所使用的容器和密封系统的知识和经验。应使用科学合理的抽样计划。样本量应基于供应商管理、包装组件规格和工艺知识等信息。

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.

真空条件下密封的容器应在开报告单/放行前预先确定的时间间隔和货架期内检测真空度维持水平。

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).

包装系统的完整性验证应当考虑任何可能对容器完整性产生负面影响的运输或装运要求（如，失压或极端温度）。

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.

如果轧盖设备产生大量非活性微粒，应当采取防止微粒污染的措施，如将此类设备放置在单独的场所并应当配置适当的抽风装置。

8.27. Vial capping of aseptically filled products can be 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.

西林瓶的轧盖可以采用灭菌后的盖以无菌操作执行，或者在无菌区外以洁净工艺完成。如果 采用后者，西林瓶应在 A 级环境保护下直至离开无菌操作区，此后已经加塞的西林瓶应在 A 级送风保护下直到完成轧盖,A 级送风的背景环境至少应满足 D 级要求。如果采用人工轧盖，则需要在适当设计的隔离器中的 A 级下进行，或在 B 级背景下的 A 级环境进行。

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.

在 A 级送风保护下采用洁净工艺对无菌灌装的无菌产品进行轧盖时，在轧盖之前，应将无塞或跳塞的西林瓶作报废处理。应使用经适当验证的自动检测方法，检测胶塞高度。

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.

当轧盖区需要人工干预时，应采用适当的技术和管理措施防止直接接触西林瓶，最大限度降低污染。RABS 和隔离器可能有助于确保所需的条件。

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.

所有注射用产品的容器在灌装后应单独对其外源性污染或是其他缺陷进行检查。缺陷分类和关键性应在确认过程中根据风险和历史知识来确定。要考虑的因素包括，但不限于缺陷对患者的潜在影响和给药途径。应对不同缺陷类型进行分类，并对批产品进行评估。与日常生产中的缺陷数量相比（基于日常和趋势数据），应对缺陷水平异常的批次进行调查。应该建立并维护所获得的已知类型缺陷的缺陷库。缺陷库可以用于生产和质量保证员工的培训。不应在合格品的后续取样和检查中发现出关键缺陷，发现出的任何关键缺陷应发起调查，因为这表明原来的检查过程可能是失败的。

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 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.
如果采用人工的方式进行检查，应当在照度和背景均受控条件下进行检查。检查速率频率应当经过适当的控制和确认。灯检人员应至少每年进行一次灯检资质确认（如果是戴眼镜的员工，应配备矫正镜片）。确认应使用生产商的缺陷库的样品组，并且考虑最差条件（如：检测时间，产品由传送带系统传递至操作员的速度，容器尺寸，或是疲劳程度），且应当包含视力检查。应尽可能地避免操作人员注意力分散，并在检查中设置适当的休息时间。

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.
如采用自动化检查方法，应验证该工艺能检测已知缺陷（可能影响产品质量或安全的缺陷）并且等于或优于手工检查方法。在设备启动前和整批内固定周期进行代表性缺陷的性能挑战。

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.
应当记录检查结果，缺陷类型和数量进行趋势分析。各类型缺陷的不合格水平应基于统计学原则进行趋势分析。当发现不良趋势时，对已上市产品的影响应作为调查的一部分进行评估。

Sterilisation 灭菌

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. 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.
如可能，产品应尽量采用经过验证并受控的灭菌工艺进行最终灭菌，因为这种灭菌工艺比经 过验证并受控的除菌过滤工艺和/或无菌加工工艺的无菌保障度更高。当产品不能经受最终灭菌时，应考虑采

用无菌加工后再进行终端热处理，并与无菌加工工艺相配合以提高无菌保障度。

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.
灭菌设备和灭菌周期/程序的选择、设计和定位应基于科学原则和数据，这些数据应证明灭菌工艺的可重复性和可靠性。所有参数均应定义，关键参数应得以控制、监测和记录。

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.
所有灭菌工艺都要进行验证。验证研究应考虑到产品的成分、储存条件以及待灭菌产品或物料从开始配置至其灭菌的最长时间。采用任何灭菌工艺前，应采用物理测量手段和生物指示剂（适用时），证明灭菌工艺适用于被灭菌的产品和设备，并证明该灭菌工艺在每种装载模式下的所有部位均能始终有效的达到预期的灭菌效果。为进行有效灭菌，所有产品、设备和部件的表面均能接受必要的灭菌处理，且灭菌工艺的设计应能确保实现有效灭菌。

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.
当所采用的是现行欧洲药典没有描述的产品灭菌方法时或当灭菌方法用于非简单的水溶液时，需要引起特殊关注。如可能，应尽量采用热力灭菌。

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.
应为所有灭菌工艺建立经过验证的装载模式，并应进行定期再验证。最大和最小装载也应被视为整体装载验证策略的一部分。

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.
灭菌工艺的有效性应根据风险，按计划的时间间隔进行回顾和验证。对于被认为是最差情况的负载模式，应以至少每年一次的最低频率开展再验证。其他负载模式应以 CCS 中合理的频率进行验证。

8.40. Routine operating parameters should be established and adhered to for all sterilisation processes, e.g. physical parameters and loading patterns.
所有灭菌工艺均应建立日常操作参数，并应遵循这些参数进行灭菌，如物理参数和装载方式。

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.
应该有适当的机制来发现不符合已验证参数的灭菌工艺。 应调查任何失败的灭菌或偏离已验证工艺的灭菌（例如，加热周期出现了阶段延长或缩短）。

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.
在恰当位置放置合适的生物指示剂（BI）应作为支持灭菌工艺验证的额外手段。BI 应按生产商说明进行保存和使用。当用 BI 来支持验证和/或监测某种灭菌工艺（如，环氧乙烷）时，每个灭菌周期均应进行阳性对照检查。如使用生物指示剂，应建立严格的预防措施来避免将 微生物污染转移至生产或其他检测过程。单独的 BI 结果不能应用于凌驾于其他关键参数和工艺设计要素。

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.
BI 的可靠性很重要。供应商应具有资质，并应控制运输和储存条件，以免影响 BI 质量。在使用新批次的 BI 之前，应确认该批次指示微生物的数量，纯度和特性。对于其他关键参数，例如 D 值和 Z 值，通常可以使用合格供应商提供的批次证书中的数值。

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.

应制定清晰区分已灭菌和未灭菌产品、设备和组件的方法。用于转移产品的容器例如筐或托 盘、设备和/或组件应清楚标识有物料名称、产品批号以及是否已灭菌的信息。应视情况使用高压灭菌指示胶带或辐照指示剂来指示某批（或亚批）物料是否已进行了灭菌。然而，这些指示剂只能显示是否进行了灭菌操作，它们不能代表产品处于无菌状态或达到了要求的无菌保障水平。

8.45. Sterilisation records should be available for each sterilisation run. Each cycle should have a unique identifier. Their conformity should be reviewed and approved as part of the batch certification/release procedure.

每次灭菌操作都要有灭菌记录。每个循环都应有唯一的识别码。这些记录的符合性应作为批放行程序的一部分进行审核和批准。

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.

各物料、设备和组件如需灭菌，应采用适用于特定材料的经过验证的方法进行。灭菌后应采取适当的保护措施以防止再污染。如果已灭菌物品在灭菌后不能立即使用，应将其保存于适当密封的包装内。应设定最长保存时限。当某组件用多层无菌袋包装时，如果无菌袋包 装的完整性和结构能够使其在被操作人员转移至 A 级区时易于消毒（例如，使用多层无菌包装袋，且每次转移到一个更高级别环境时，脱去一层），则其不需要储存在洁净区内。当用密封袋包装来实现保护时，应在灭菌前就实施包装操作。

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.

当将物料、设备、组件和辅助物品装于密封容器内灭菌后转移至 A 级区时，该过程应采用适当的，经验证的方法（例如，气锁（气闸）或传递窗）并能对密封容器的外表面进行消毒。还应考虑使用快速传递接口技术。应证明这些方法能有效控制对 A/B 级区的环境造成污染 的潜在风险。同样，应证明消毒方法能将包装上的任何污染有效降低至进入 A/B 级区的可接受水平。

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.

当将物料、设备、组件和辅助物品置于密封包装或容器内灭菌时，包装应确认以最大限度地 减少微粒、微生物、内毒素/热原或化学污染的风险，并与所选的灭菌方法兼容,包装密封工艺应经过验证。验证应考虑无菌保护屏障系统的完整性以及灭菌前的最长保存时间和设置给已灭菌物品的最大货架寿命。在使用前，应确认每个灭菌物品的无菌保护屏障系统的完整性。

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 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.

用于非直接或间接产品接触部件且无菌加工必需但不能灭菌的材料、设备、部件和辅助物品，应建立有效的经过验证的消毒和转移程序。一旦对这些物品进行消毒，应采取防护措施以防止再污染。这些物品以及其他代表潜在污染途径的物品，应被加入环境监测程序中。

Sterilisation by heat 热力灭菌

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).

每个加热灭菌周期应以电子方式或通过纸质方式以适当的准确度和精确度记录在设备上。监测系统应

独立于，应在控制和监控系统中具有安全措施和/或冗余配置，以检测不符合经验证的循环参数要求的循环并中止或判定该循环失败（例如，独立的控制和监控系统使用复合式/双线探头）。

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.
用于控制和/或记录的温度探头的位置应在验证期间确定，并根据系统设计进行选择，以便正确记录和表示常规循环条件。验证研究应旨在证明系统控制和记录探头位置的适用性，并应包括在验证期间使用位于同一位置的独立监测探头验证这些探头的功能和位置.

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.
在开始计算灭菌时间之前，整个负载应达到要求的温度。对于在负载内使用参考探头控制的灭菌周期，应特别注意确保在灭菌段开始之前将负载探头的温度控制在规定的温度范围内。

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.
热力灭菌周期的高温阶段结束后，应采取预防措施防止灭菌后的装载物在冷却阶段被污染。任何接触产品或已灭菌物品的冷却液或气体均应进行灭菌。

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.
在允许进行参数放行的情况下，应采用耐受性好的系统来进行产品生命周期验证以及生产工艺的日常监控。该系统应进行周期性回顾。附录 17 中有更多关于参数放行的指南。

Moist heat sterilization　湿热灭菌

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 containers that may be damaged by other cycle designs (e.g. Blow –Fill –Seal containers,

plastic bags).

湿热灭菌可以使用蒸汽（直接或间接接触）实现，但也包括其他系统，如过热水系统（喷淋或浸没循环），可用于可能因其他方式灭菌容器（例如 吹灌封容器、塑料袋）被破坏的情况。

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 dryness should be confirmed by visual inspection as a part of the sterilisation process acceptance.

除密封容器中的产品外，要灭菌的物品应干燥，包装在保护屏障系统中，该系统允许去除空气和蒸汽，并防止灭菌后再次污染。 从灭菌器中取出后，所有装载的物品都应干燥。作为灭菌过程验收的一部分，应通过目视检查确认负载干燥度。

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.

对于多孔（坚硬物品）循环来说，应使用时间、温度和压力来监测灭菌过程并记录。每个灭菌后的物品均应检查其是否损坏，包装材料的完整性，以及从灭菌柜中取出是是否有水分。任何不符合预期目的的物品均应移出生产区，并应进行调查。

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.

对于能够进行抽真空灭菌循环的高压灭菌器，应在整个灭菌期间记录腔室排水口的温度。在适当的情况下也可以使用装载探头，但控制系统应保持与装载验证相关。对于在线蒸汽灭 菌（SIP）系统，还应记录各冷凝水排水点在整个灭菌周期内的温度。

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 F0. Critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilisation validation and routine cycle acceptance criteria.

多孔物品灭菌周期的验证应包括对平衡时间、暴露时间、压力与温度的相关性以及暴露过程中最小/最大温度范围，而液体物品灭菌周期的验证应考虑温度、时间和 F0 值。应确定这些关键参数的限度（包括适当的允差）并将其作为灭菌验证和常规灭菌接受标准的一部分进行确认。

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.
当灭菌周期的某个阶段为真空阶段，或者系统在灭菌后回到或者低于周围环境压力时，灭菌系统应定期进行泄漏测试（通常每周）。

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.
当灭菌程序包括空气排除（如，高压灭菌器多孔物品装载、冻干机）时，应在灭菌前和灭菌过程中确保充分排除空气。对于高压灭菌器，应当有空气移除测试程序（BD 测试）（通常每天进行）或空气检测器系统。待灭菌装载物的设计应能保证有效的排除空气，并便于排水以防止冷凝水的聚集。

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).
应通过适当的灭菌循环设计和控制（例如设置正确的压力，升降温速率和装载模式）来防止最终灭菌的非刚性容器（例如通过吹 –灌 –封或成型 –灌 –封技术生产的容器）的变形和损坏。

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 to use.
当使用了在线灭菌（SIP）系统时（例如，对于固定的管路、储罐和冻干机），该系统应进行适当的设计和验证以确保对系统的所有部分均进行了必要的处理。日常使用中应对系统恰当位置的温度、压力和时间进行监测，这是为了确保所有区域均进行了有效的和可重现的灭菌；首次和日常验证中应证明这些位置具有代表性，且和升温最慢的位置相关联。一旦系统经 SIP 灭菌后，应在使用前保持其完整性并有正压保护,否则应在使用前重新灭菌。

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.
在使用过热水作为传热介质的流体负载循环中，热水应始终达到所有要求的接触点。首次温度确认研究应包括全部装载的温度分布。应该对设备进行日常检查，以确保喷嘴（喷入水的地方）没有被阻塞，并且排水管中没有碎屑。

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.
过热水高压灭菌器中液体装载的灭菌验证应包括整个装载的温度分布以及热渗透和重现性研究。负载的所有部分应均匀加热，并在规定的时间内达到所需的温度。常规温度监测探头应与确认过程中确定的最差情况位置相关联。

Dry heat sterilization　干热灭菌

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 in an oven or in a continuous tunnel process, e.g. for sterilisation and depyrogenation of glass containers.
干热灭菌利用高温空气或气体对产品或物品进行灭菌。干热灭菌特别适用于热去除难以消除的耐热污染物，例如内毒素/热原，通常用于准备无菌灌装组件。当在设定的范围内进行日常灭菌操作时，产品、部件和设备所暴露的时间和温度的组合应能产生足够的且可重现的致 死水平和/或内毒素/热原灭活/去除水平。该工艺可以在烘箱中或在连续隧道工艺中进行，例如在烘箱中进行玻璃容器的灭菌和除热原。

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:

干热灭菌/去热原隧道烘箱应配置成能维持从较高级别区域到较低级别区域的压力差和气流，从而保证 A 级区的完整性和性能。气流模式应进行评估。应评估任何气流变化的影响，以确保维持灭菌曲线。供应给隧道的所有空气均应至少通过 HEPA 过滤器，并应至少每半年一次测试以证明空气过滤器的完整性。应对任何接触灭菌后组件的隧道烘箱的部件进行适当的灭菌或消毒。验证和/或日常操作时应考虑的关键工艺参数应包括，但不限于：

i. Belt speed or dwell time within the sterilising zone.
传送带速度或在灭菌区的滞留时间。

ii. Temperature – minimum and maximum temperatures.
温度——最低和最高温度。

iii. Heat penetration of the material/article.
物品/组件的热穿透。

iv. Heat distribution/uniformity.
热分布/均匀性。

v. Airflows determined by air pressure difference profiles correlated with the heat distribution and penetration studies.
压差导致的气流流型与热分布和热穿透研究相关。

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.
当对任何组件或接触产品设备/物料使用加热工艺进行除热原处理时，应进行验证研究证明 该工艺有合适的 F_h 值，并至少能降低 3 个对数值的内毒素。当达到这一点时，在这些情况下没有额外的要求证明达到灭菌要求。

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.

在验证过程中应使用添加了内毒素的容器，并通过完整的物料平衡控制管理。容器应能代表材料正常加工（关于包装材料的成分、孔隙率、尺寸、标称体积）。还应证明内毒素定量和回收物料平衡。

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:
干热灭菌柜通常用于内包装组件、起始物料或活性物质的灭菌或去热原，也可用于其它工艺。在整个灭菌和灭菌后保持过程中，干热灭菌柜应该相对于较低等级区域维持正压力，除非能够维持包装完整性。所有进入烘箱的空气应通过高效过滤器。验证确认和/或日常操作过程中应考虑的关键工艺参数应包括，但不限于：

i. Temperature.
温度

ii. Exposure period/time.
暴露时间

iii. Chamber pressure (for maintenance of over pressure).
腔室内压力（维持过压）

iv. Air speed.
风速

v. Air quality within the oven.
箱体内空气质量

vi. Heat penetration of material/article (slow to heat spots).
物料/物品的热穿透（升温较慢的点）

vii. Heat distribution/uniformity.
热分布/均匀度

viii. Load pattern and configuration of articles to be sterilised/depyrogenated including minimum and maximum loads.
待灭菌/除热原物品的装载模式和配置，包括最小和最大装载量

Sterilisation by radiation　辐照灭菌

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.
辐照灭菌主要用于热敏感物料和产品的灭菌。紫外照射是不可接受的灭菌方法。有关电离辐照灭菌的指南可在附件 12 中找到。

8.72. Validation procedures should ensure that the effects of variation in density of the product and packages are considered.
验证程序应确保考虑到了不同产品密度和包装变化的影响。

Sterilisation with ethylene oxide　环氧乙烷灭菌

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.
只有当其他方法不可行时才能使用本方法。在工艺验证过程中，应证明对产品没有破坏效果，以及排气的条件和时间可将任何残留的环氧乙烷（EO）气体和反应产物降低至既定产品和物料的可接受范围内.

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.
气体和微生物细胞之间的直接接触是至关重要的，应采取预防措施避免可能包裹在物料（如晶体和干蛋白）中的微生物出现。包装材料的性质、孔隙度和数量可显著影响灭菌工艺。

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.
暴露于气体之前，应使物料平衡至灭菌工艺所要求的温湿度条件下。在使用蒸汽对装载进行灭菌处理的情况下，它应具有适当的质量。此过程所需要的时间应尽可能和缩短灭菌前放置时间的要求做权衡。

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.
每个灭菌循环应使用适当的生物指示剂进行监测，应将适当数量的生物指示剂分布在装载验证输出并定义为最差点的位置。

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:
灭菌工艺验证和日常监控中应考虑的关键工艺参数包括，但不限于：

i. EO gas concentration.
EO 气体浓度

ii. Pressure.
压力

iii. Amount of EO gas used.
EO 气体的使用量

iv. Relative humidity.
相对湿度

v. Temperature.
温度

vi. Exposure time.
暴露时间

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.
灭菌完成后，应对装载物进行通气，以使 EO 气体和/或其反应产物从包装产品中释放出来，并达到预期水平。通气可在灭菌柜和/或独立的通气柜或通气室中进行。通气阶段应作为整个 EO 灭菌工艺验证的一个部分来进行验证。

Filter sterilisation of products which cannot be sterilised in their final container
非最终灭菌产品的除菌过滤

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 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).
如果产品不能在最终容器中进行灭菌，那么溶液或液体需要通过一个无菌过滤的方式（经过 适当的验证的孔径最大为 0.22µm，以获得无菌滤液）来进行灭菌，随后被无菌灌装至已预先灭菌的容器内。滤器的选择应当确保与产品是相容的，并符合其上市申请文件的描述（详见 8.135）。

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.
生产过程中可在多个地方使用适当的降低生物负载的预过滤器和/或除菌级的过滤器，以确保在最终除菌级滤器前的液体的生物负载处于较低的且受控的水平。和其他灭菌工艺相比，由于无菌过滤工艺存在潜在的额外风险，在灌装前面通过一个尽可能靠近灌装位置的无菌的除菌过滤器进行的额外过滤应被考虑将作为整个 CCS 过程的一部分。

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 affected by the product to be filtered. Adsorption of product components and extraction/leaching of filter components should be evaluated (see paragraph 8.135).
过滤系统组件的选择，以及它们在过滤系统内的相互连接和布置方式，包括预过滤器，应建立在产品关键质量属性的基础上，并加以证明和记录。过滤系统应尽量减少纤维和微粒的产生，不会引起或造成杂质的不可接受水平，或改变产品质量和功效的工艺特性。同样的，过滤器特性应当与流体相匹配，待过滤产品不得对过滤器特性产生负面影响。应对产品组分吸 附和过滤器组件的溶出/析出进行评估（详见 8.135）。

8.82. The filtration system should be designed to:
过滤系统应被设计为：

i. Allow operation within validated process parameters.
允许在经验证的工艺参数范围内进行操作。

ii. Maintain the sterility of the filtrate.
维持滤液的无菌性。

iii. Minimize the number of aseptic connections required between the final sterilising grade filter and the final filling of the product.
最小化最终除菌级别过滤器和产品最终灌装之间的无菌连接的次数。

iv. Allow cleaning procedures to be conducted as necessary.
允许在必要时进行清洁程序。

v. Allow sterilisation procedures, including sterilisation in place, to be conducted as necessary.
允许在必要时进行包括 SIP 在内的灭菌程序。

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.
允许在必要时在过滤之前和之后对 0.22 µm 最终除菌级过滤器进行在线完整性测试，最好作为一个密闭系统，选择在线完整性测试方法，以避免对产品质量产生任何不利影响。

8.83. Sterile filtration of liquids should be validated in accordance with relevant Pharmacopeia requirements. Validation can be grouped by different strengths or variations of a product but should be done under worst –case conditions. The rationale for grouping should be justified and documented.
液体的除菌过滤应当按照相关药典的要求进行验证。验证可按产品的不同规格或种类进行分组，但应当在最差情况下进行。应证明分组的合理性并记录。

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.
过滤器验证期间，如可行，应使用待过滤产品进行除菌级滤器的细菌截留测试。当待过滤产品不适用于细菌截留测试时，应采用合适的替代产品用于测试并说明原因。应论证在细菌截留测试中所用的挑战微生物。

8.85. Filtration parameters that should be considered and established during validation should include, but are not limited to:
验证过程中应考虑和确定的过滤参数，应包括但不限于：

i. The wetting fluid used for filter integrity testing:
用于过滤器完整性测试的润湿液：

- 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.
用于过滤器完整性测试的润湿液应当基于滤器供应商的建议或为待过滤液体。应建立适当的完整性测试值的标准。

- 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.
如果用产品外的其他液体对系统进行冲洗或进行现场完整性测试，应采取适当的措施，以避免对产品质量产生任何有害影响。

ii. Filtration process conditions including:
过滤工艺条件包括：

- Fluid pre –filtration holding time and effect on bioburden.
预过滤液体的保存时间和对生物负载的影响

- Filter conditioning, with fluid if necessary.
如有必要，用液体对过滤器进行润湿。

- Maximum filtration time/total time filter is in contact with the fluid.
最长过滤时间/过滤器接触液体的总时间。

- Maximum operating pressure.
最大操作压力

- Flow rate.
流速

- Maximum filtration volume.
最大过滤量

- Temperature.
温度

- The time taken to filter a known volume of bulk solution and the pressure difference to be

used across the filter.
过滤已知量散装溶液所用时间和过滤时过滤器两端的压差。

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.
应实施常规过程控制以确保遵循经过验证的过滤参数。关键工艺参数的结果应包含在批次记录中，包括但不限于过滤已知体积的散装溶液所需的最短时间和过滤器上的压差。应记录和调查生产过程中与关键参数的任何显著差异。

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 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:
已灭菌过滤器组件的完整性应在使用前通过完整性测试（使用前灭菌后完整性测试，PUPSIT），以检查由于过滤器使用前的准备造成的完整性破坏或降低。用于进行液体除菌的除菌级滤器应当在使用后进行无破坏的完整性测试，然后再将滤器从滤壳中取出。完整性测试方法应经过验证，测试结果应当与过滤器在验证期间建立的微生物截留能力关联起来。使用的测试实例包括起泡点法，扩散流发，水侵入法或压力保持试验。通常认为，由于工艺的限制（例如过滤非常小体积的溶液），PUPSIT 并不能总是在灭菌后进行。在这样情况下，可采取替代方法，前提是已经进行了全面的风险评估，并通过实施适当的控制措施来实现合规，以降低过滤系统完整性损失的风险。在进行风险评估时应考虑的事项应包括但不限于:

i. In depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized.
对过滤器灭菌工艺的深入了解和控制，以确保对过滤器的潜在损坏被降到最低。

ii. In depth knowledge and control of the supply chain to include:

对供应链的深入了解和控制，包括:

- Contract sterilisation facilities.
  委托灭菌设施
- Defined transport mechanisms.
  明确的运输机制
- Packaging of the sterilised filter, to prevent damage to the filter during transportation and storage.
  对灭菌后的过滤器进行包装，防止在运输和储存过程中损坏过滤器。

iii. In depth process knowledge such as:
对工艺的深入了解，例如：

- 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.
  具体的产品类型，包含颗粒负荷和是否存在任何影响滤器完整性数值的风险，比如可能改变滤器完整性测试值，从而无法在使用后完整性检测过程中检测到非完整的过滤器。
- 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.
  在最终除菌级过滤器前，通过预过滤和操作步骤，可以在除菌过滤前清除微粒负载并净化产品。

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.
关键的无菌气体和排气过滤器（直接与产品的无菌性相关联）的完整性应当在使用后通过测试证明，且过滤器应保持在过滤器组件或滤壳中。

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).
非关键的空气或气体过滤器的完整性应以适当的间隔进行确认并记录。如果气体过滤器的持续使用时

间较长，则应在安装过程和替换前进行完整性测试。应根据风险规定和监测最长使用期限（例如适当时考虑允许的最大使用次数和热处理/灭菌周期）。

8.90. For gas filtration, unintended moistening or wetting of the filter or filter equipment should be avoided.
当气体过滤时，应避免过滤器或过滤设备的意外潮湿或润湿。

8.91. If the sterilising filtration process 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 sterilising unit and all filters within the system should satisfactorily pass integrity testing after use.
如果除菌过滤工艺是通过一个为实现给定液体无菌性要求而由多个过滤器组成的系统来被验证的，那么这个系统被认定为是一个单一除菌单元，并且系统内所有的过滤器都应当在使用后满意的通过完整性测试。

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.
在冗余过滤系统中（存在备用的第二个冗余除菌级别过滤器，但除菌工艺验证仅要求一个过滤器），应执行主除菌过滤器使用后的完整性测试，如果主除菌级别过滤器被证明是完整的，则不需要对备用冗余过滤器进行使用后的完整性测试。然而，如果主过滤器使用后的完整性测试失败，则应针对备用冗余过滤器开展使用后完整性测试，同时应针对主过滤器的完整性测试失败开展根本原因调查和风险评估。

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.
生物负载的样品应取自散装产品，并在最终除菌过滤前即时取样。如果使用了冗余的过滤装置，则应在第一个过滤器之前进行取样。取样系统的设计不得引入污染。

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.
液体除菌过滤器应在单批操作完成后废弃，并且同一个过滤器的连续使用应不得超过 1 个工作日，除非进行过验证。

8.95. Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:
在产品阶段性生产过程在 CCS 中已被适当的证明和验证后，过滤器使用人员应当：

i. Assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid.
评估并记录为给定液体进行除菌过滤的过滤器的持续使用时间相关的风险。

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.
执行并记录有效的验证和确认研究，以证明在给定的除菌过滤过程和给定的液体中过滤器的使用时间不会影响最终除菌级过滤器的性能和滤液质量。

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.
记录经验证的过滤器最长使用时间，并实施控制措施，确保过滤器的使用时间不超过经验证的最长有效使用时间。这些控制的记录应予以保留。

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.
实施控制措施，确保被液体或清洗剂残留物污染的过滤器，或被认为有任何其他缺陷的过滤器不再使用。

Form –Fill –Seal (FFS)　成型 –灌 –封

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 Annex.
用于最终灭菌产品的 FFS 设备的条件应符合本附录 8.3 和 8.4 的环境要求。用于无菌生产的 FFS 设备的条件应符合本附录 8.10 段的环境要求。

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.
在组件制造、供应和处理过程中，应通过适当的控制将 FFS 工艺中使用的包装薄膜的污染降至最低。由于包装薄膜的重要性，应实施程序以确保所提供的薄膜符合规定的标准并具有适当的质量，包括材料厚度和强度、微生物和微粒污染、完整性和相关的样稿。应在 PQS 中定义和控制包装薄膜和相关组件的取样频率、生物负载和（如适用）内毒素/热原水平，并在 CCS 中加以考虑。

8.98. Particular attention should be given to understanding and assessing the operation of the equipment, including set –up, filling, sealing and cutting processes, so that critical process parameters are understood, validated, controlled and monitored appropriately.
应特别注意理解和评估设备的操作，包括装配、灌装、密封和切割过程，以便正确理解、验证、控制和监测关键过程参数。

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.
任何与产品接触的气体，例如：用于给容器充气或用作产品填充的气体应在尽可能靠近使用点的位置进行适当过滤。应根据 6.18 和 6.19 定期验证所用气体的质量和气体过滤系统的有效性。

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:
在 FFS 确认期间确定的控制措施应与 CCS 保持一致。需要考虑的方面包括但不限于:

i. Determination of the boundaries of the critical zone.
确定关键区域的边界。

ii. Environmental control and monitoring, both of the machine and the background in which it is placed.
环境控制和监测，包括设备和它所在的背景。

iii. Personnel gowning requirements.
人员更衣要求。

iv. Integrity testing of the product filling lines and filtration systems (as relevant).
产品灌装线和过滤系统的完整性测试（如相关）。

v. Duration of the batch or filling campaign.
批次或灌装活动的持续时间。

vi. Control of packaging films, including any requirements for film decontamination or sterilisation.
包装薄膜的控制，包括对薄膜去污或灭菌的任何要求。

vii. Cleaning –in –place and sterilisation –in –place of equipment as necessary.
必要时对设备进行在线清洗和在线灭菌。

viii. Machine operation, settings and alarm management (as relevant).
设备操作、设置和报警管理（如相关）。

8.101. Critical process parameters for FFS should be determined during equipment qualification and should include, but are not limited to:
FFS 的关键工艺参数应在设备确认期间确定，并应包括但不限于：

i. Settings for uniform package dimensions and cutting in accordance with validated parameters.
根据验证的参数设置统一的包装和裁切尺寸。

ii. Setting, maintenance and monitoring of validated forming temperatures (including pre –heating and cooling), forming times and pressures as relevant.
设置、维护和监控经过验证的相关成型温度（包括预热和冷却）、成型时间和压力。

iii. Setting, maintenance and monitoring of validated sealing temperatures, sealing temperature uniformity across the seal, sealing times and pressures as relevant.
设置、维护和监控已验证的密封温度、整个密封的密封温度均匀性、密封时间和压力。

iv. Environmental and product temperature.
环境和产品温度、

v. Batch –specific testing of package seal strength and uniformity.
包装密封强度和均匀性的批次特定测试。

vi. Settings for correct filling volumes, speeds and uniformity.
正确灌装量、速度和均匀度的设置。

vii. Settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity is not compromised.

任何额外印刷（批号）、凹凸压纹的设置，以确保包装完整性不受影响、

viii. Methods and parameters for integrity testing of filled containers (see paragraph 8.22).
灌装容器完整性测试的方法和参数（详见 8.22）、

8.102. Appropriate procedures for the verification, monitoring and recording of FFS critical process parameters and equipment operation should be applied during production.
在生产过程中应采用适当的程序来验证、监控和记录 FFS 关键工艺参数和设备操作。

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.
操作程序应描述如何检测和纠正成型和密封问题，被判定为不合格的包装或密封问题应记录和调查。

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.
应根据风险制定适当的维护程序，包括对包装密封有效性至关重要的工具的维护和检查计划。任何识别出的表明潜在产品质量问题的问题都应记录在案并进行调查。

Blow –Fill –Seal　吹 –灌 –封

8.105. Blow –Fill –Seal equipment used for the manufacture of products which are terminally 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.
用于生产最终灭菌产品的吹灌封设备应安装在至少 D 级环境中。灌装区域的条件应符合 8.3 和 8.4 的环境要求。

8.106. BFS used for aseptic processing:
BFS 用于无菌工艺：

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.
用于无菌灌装的往复式设备，模具对环境是开放的，因此模具挤出、吹塑和密封的区域在关键区域应满足 A 级条件。灌装环境的设计和维护应满足 A 级条件，静态和动态的活性粒子和总粒子数均需满足限度要求。

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 designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.
对于用于无菌灌装的旋转式设备，通常包材吹塑一旦形成就与环境封闭，包材内的灌装环境的设计和维护应满足静态和动态的活性粒子和总粒子数满足 A 级要求。

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.
如果使用 A/B 级洁净服，设备应至少安装在 C 级环境中。在 C 级区域对穿着 A/B 级服装的操作人员进行微生物监测时，应按照风险管理原则进行，并考虑到这些操作人员所从事的活动而适用的限值和监测频率。

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.
由于在运行过程中聚合物挤出和切割会产生微粒，以及 BFS 设备关键灌装区的尺寸限制，因此预计不会对 BFS 设备的总粒子进行动态监测。但是，应提供数据来证明设备的设计可确保灌装过程环境的关键区域在操作中满足 A 级条件。

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.
BFS 工艺的微生物环境监测应基于风险，并根据本附录第 9 节进行设计。应在关键操作的整个过程中进行动态活性粒子监测，包括设备组装。对于旋转式 BFS 设备，可能无法监控关键灌装区。

8.109. The environmental control and monitoring 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.

环境控制和监测计划应考虑 BFS 工艺产生的活动部件和复杂的气流路径以及工艺的高热量输出的影响（例如，通过使用气流可视化研究和/或其他等效研究）。环境监测计划还应考虑空气过滤器配置、空气过滤器完整性、冷却系统完整性（详见 6.21）、设备设计和确认等因素。

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.

在成型容器的挤出、成型或密封过程中与容器关键表面接触的空气或其他气体应经过适当的过滤。应根据 6.18 和 6.19 定期验证所用气体的质量和气体过滤系统的有效性。

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.

应通过聚合物颗粒储存、取样和分配系统的适当设计、控制和维护来防止聚合物颗粒被微粒和微生物污染。

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.

应了解和验证挤出系统为成型容器提供适当无菌保证的能力。原料聚合物的取样频率、生物负载和（如适用）内毒素/热原水平应在 PQS 中定义和控制，并在 CCS 中加以考虑。

8.113. Interventions requiring cessation of filling 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).

要求停止灌装和/或挤出、成型和密封以及在需要时对灌装机进行重新灭菌的干预措施应在灌装程序中明确定义和描述，并酌情包含在 APS 中（详见 9.34、9.35 和 9.36）。

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:

BFS 设备确认过程中识别出来的控制措施应与工厂的 CCS 一致，需要考虑的方面包括但不限于：

i. Determination of the boundaries of the critical zone.

确定关键区域的边界

ii. Environmental control and monitoring, both of the machine and the background in which it is placed.
环境控制和监测，包括设备以及设备所处的背景环境

iii. Personnel gowning requirements.
人员更衣要求

iv. Integrity testing of the product filling lines and filtration systems (as relevant).
产品灌装线和过滤系统的完整性测试（如相关）

v. Duration of the batch or filling campaign.
批次或灌装操作的持续时长

vi. Control of polymer granulate, including distribution systems and critical extrusion temperatures.
控制聚合物颗粒，包括分配系统和关键挤出温度

vii. Cleaning –in –place and sterilisation –in –place of equipment as necessary.
必要时对设备进行在线清洁和在线灭菌。

viii. Machine operation, settings and alarm management (as relevant).
设备操作、设置和报警管理（如相关）。

8.115. Critical process parameters for BFS should be determined during equipment qualification and should include, but are not limited to:
BFS 的关键工艺参数应在设备确认期间确定，并应包括但不限于：

i. Clean –in –place and sterilisation –in –place of product pipelines and filling needles (mandrels).
产品管道和灌装针（芯轴）的在线清洁和在线灭菌。

ii. Setting, maintenance and monitoring of extrusion parameters, including temperature, speed and extruder throat settings for parison thickness.
挤出参数的设置、维护和监控，包括温度、速度和模坯厚度的挤出机关键设置。

iii. Setting, maintenance and monitoring of mould temperatures, including rate of cooling where necessary for product stability.
模具温度的设置、维护和监控，包括产品稳定性所需的冷却速度。

iv. Preparation and sterilisation of ancillary components added to the moulded unit, e.g. bottle caps.

添加到成型单元的辅助组件的制备和灭菌，例如：瓶盖。

v. Environmental control, cleaning, sterilisation and monitoring of the critical extrusion, transfer and filling areas as relevant.
关键挤出、转移和灌装区域的环境控制、清洁、灭菌和监控（如相关）。

vi. Batch –specific testing of package wall –thickness at critical points of the container.
在容器的关键点对包装壁厚进行批次测试。

vii. Settings for correct filling volumes, speeds and uniformity.
正确灌装量、速度和均匀度的设置。

viii. Settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity and quality is not compromised.
任何额外印刷（批号）、凹凸压纹的设置，以确保单元完整性和质量不受影响。

ix. Methods and parameters for integrity testing of 100% of all filled containers (see paragraph 8.22).
100% 灌装容器完整性测试的方法和参数（详见 8.22）。

x. Settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).
用于去除灌装单元周围的废塑料（去除毛边）的切割器或冲压机的设置。

8.116. Appropriate procedures for the verification, monitoring and recording of BFS critical process parameters and equipment operation should be applied during production.
在生产过程中应采用适当的程序来验证、监控和记录 BFS 关键工艺参数和设备操作。

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.
操作程序应描述如何检测和纠正吹气、成型和密封问题。被判定为不合格的包装或密封问题应记录和调查。

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 appropriately decontaminated and added to the process using a clean, controlled process.
如果 BFS 工艺包括向成型容器添加组件（例如，为 LVP 瓶添加瓶盖），这些组件应进行适当的去污处理，并采用清洁、受控的过程添加到工艺中。

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.
对于无菌工艺，应在 A 级条件下添加组件，以使用预先灭菌的组件确保关键表面的无菌性。

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.
对于最终灭菌的产品，最终灭菌工艺的验证应确保组件和成型容器之间的所有关键产品通道的无菌性，包括灭菌期间未润湿的区域。

iii. Testing procedures should be established and validated to ensure the effective sealing of components and moulded containers.
应建立并验证测试程序以确保组件和成型容器的有效密封。

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.
应根据风险制定适当的维护程序，包括对单元密封、完整性和无菌性至关重要的物品的维护和检查计划。

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.
用于成型容器的模具是非常关键的设备，对其所做的任何的变更或修改均应评估其对成品容器完整性的影响，并通过验证支持。任何已识别的表明潜在产品质量问题的问题应记录在案并进行调查。

Lyophilization 冷冻干燥

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.
冷冻干燥是一个关键工艺步骤，所有可能影响产品或物料无菌性的活动都需要被视为灭菌后产品的无菌操作的延伸。冻干设备和其工艺的设计应能确保产品或物料在冻干期间无菌性的保持，防止用于冻干的产品灌装和冻干工艺结束之间的微生物和微粒污染。所有在线控制措施应由工厂的 CCS 决定。

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.
冻干机和相关设备（例如托盘、西林小瓶支撑环）的灭菌应经过验证，并在 APS 期间适当的挑战灭菌循环和使用之间的保持时限（详见 9.33）。冻干机应基于系统设计进行定期灭菌。在维护和清洁后应进行再灭菌。应防止灭菌后的冻干机和相关设备在灭菌后受到污染。

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 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.
冻干机和相关的产品转移和装载/卸载区域的设计应尽可能减少操作员的干预。冻干机灭菌的频率应根据使用过程中与系统污染相关的设计和风险来确定。手动装载或卸载且没有屏障技术分离的冻干机应在每次装载前进行灭菌。对于由自动化系统装载和卸载或由封闭屏障系统保护的冻干机，应证明灭菌频率是合理的，并作为 CCS 的一部分记录在案。

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.
灭菌后以及冻干过程中应维持冻干机系统的完整性。用于维持冻干机完整性的过滤器应在每次使用前进行灭菌，且过滤器完整性测试结果应作为批放行证明的一部分。冻干机腔体的真空/泄露完整性测试的频率应当被记录，进入冻干机的最大允许空气泄漏率应有规定并在每次冻干循环开始时进行检查。

8.125. Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.
应周期性检查冻干托盘以确保其无变形或损坏。

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:
装载（如果冻干后物料仍未密封并暴露，还包括卸载）设计要考虑的要点包括但不限于:

i. The loading pattern within the lyophilizer should be specified and documented.
应规定并记录冻干机的装载方式、

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 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).
将半封闭容器转运至冻干机时，需要始终在 A 级条件下并设计一种能够最小化操作员直接干扰的方式来进行。应使用诸如传送带系统或便携式转移系统（例如，洁净空气传输车，便携式单向流工作台）等技术，以确保能够维持用于转运部分密闭容器的系统的洁净度。或者，如经过验证，可以使用在 A 级区密闭且在 B 级区不再次打开的托盘以保护半压塞的西林（例如：适当密封的箱子）。

iii. Airflow patterns should not be adversely affected by transport devices and venting of the loading zone.
气流流型应不受运输装置和装载区域通风的影响。

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.
未密封的容器（例如未完全半压塞的西林瓶）应保持在 A 级条件下，且通常应通过物理隔离技术或其他适合的措施与操作员隔离。

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.
在冻干机打开前，若产品处于半压塞状态，则产品移出冻干机进行下一步操作时应保持在 A 级条件下。

vi. Utensils used during loading and unloading of the lyophilizer (e.g. trays, bags, placing devices, tweezers) should be sterile.
用于冻干机装载和卸载的工具（例如:托盘、袋子、定位装置、镊子）应无菌。

Closed systems　密闭系统

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.

密闭系统的使用可以减少来源于相邻环境的微生物、粒子和化学污染的风险。密闭系统的设计应能始终减少人工操作及相关风险。

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).

保证用于无菌操作的密闭系统的所有产品接触表面的无菌性是非常关键的。用于无菌工艺的密闭系统的设计和选择应当确保无菌性的保持。最终灭菌过滤器后的用于连接无菌设备（如管子与管路）与已灭菌产品通道的管路应设计为无菌连接的方式，例如通过内在的无菌连接装置。

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.

应有适当的措施以确保用于无菌连接的组件的完整性。应在 CCS 中确定并记录所使用的方式。当有损害产品无菌性的风险时，应考虑适当的系统完整性测试。供应商评估应包含对可能导致系统无菌性失败的潜在失败模型有关的数据进行收集。

8.130. The background environment in which closed systems are located should be based on their design 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).

密闭系统所处的背景环境应基于其设计以及使用的工艺。对于无菌工艺，如果当有系统完整性可能受损的风险时，则应将其放置在 A 级区域中。如果可以表明该系统在每次使用时都能保持完整性（例如通过压力测试和/或监测），则有可能将其放置在级别较低的环境中。应彻底评估不同级别区域之间的任何转移（详见 4.10）。如果密闭系统被打开（例如对散装生产线进行维护），则应在于物料相适当的洁净区内执行（例如，对于终端灭菌工艺，在 C 级区，对于无菌操作，在 A 级区），或者进行后续清洁和消毒（如果是无菌工艺，则灭菌）。

Single use systems (SUS)　一次性使用系统（SUS）

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.
一次性使用系统（SUS）是用于无菌产品生产的技术，替代重复使用设备。SUS 可以是单一组件，也可以是由多个组件制成，例如袋子、过滤器、管路、接头、阀门、储存瓶和传感器。一次性系统的设计应减少对操作的需求和人工干预的复杂性。

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:
与 SUS 有关的一些特定风险，应作为 CCS 的一部分进行评估，包括但不限于：

i. The interaction between the product and product contact surface (such as adsorption, or leachables and extractables).
产品与产品接触表面的相互作用（例如吸附、浸出物和溶出物）、

ii. The fragile nature of the system compared with fixed reusable systems.
与固定的重复使用系统相比的脆弱属性。

iii. The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made.
增加了人工操作（包括对系统的检查和处理）和产生的连接的数量和复杂程度。

iv. The complexity of the assembly.
装配的复杂程度、

v. The performance of the pre – and post –use integrity testing for sterilising grade filters (see paragraph 8.87).
除菌级过滤器使用前后完整性测试的性能（详见 8.87）、

vi. The risk of holes and leakage.
小孔和泄露的风险、

vii. The potential for compromising the system at the point of opening the outer packaging.

打开外包装时对系统的潜在影响、

viii. The risk of particle contamination.
微粒污染的风险、

8.133. Sterilisation processes for SUS should be validated and shown to have no adverse impact on system performance.
SUS 的灭菌工艺应经过验证，并对系统性能没有负面影响。

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.
一次性使用系统（包括灭菌）的供应商评估对于这类系统的选择和使用是至关重要的。对于无菌 SUS，无菌保证的确认应作为供应商确认的一部分，每个单元的灭菌证据应在接收时进行检查。

8.135. The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions.
应在工艺条件下评估产品和与产品接触表面的吸附和反应。

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.
应当评估 SUS 的溶出物和吸附物，以及对产品质量的影响，尤其是当 SUS 系统是由高分子材料制造时。应评估每一个组件溶出物数据的适用性。对于被认为有吸附物高风险的组件，包括那些可能吸附被加工的物料或有较长的物料接触时间的组件，应考虑对可浸出物的研究进行评估，包括对安全性问题的考虑。如果采用模拟工艺条件，应能准确反映实际工艺条件并基于科学原理。

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 mechanically sealed) remain integral under

these conditions.

SUS 的设计应能在预期的操作条件下整个工艺期间保持完整性。在日常加工或运输过程可能出现暴露于极端条件（例如冻融过程）的情况，应当注意一次性使用组件的结构完整性，包括在这些条件下保持其固有无菌连接装置（包括热封和机械密封）完整性的确认。

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.

应当为 SUS 建立并实施与风险或产品及其工艺的关键程度相适当的可接受标准。接收时， 应检查每一件 SUS，确保其是按照批准的质量标准进行生产、供应和发运的。应当在使用前对外包装（例如外箱、产品保护袋的外观）、标签打印和附属文件的审核（例如符合性证书、灭菌证明）进行目视检查并记录。

8.139. Critical manual handling operations of SUS such as assembly and connections should be subject to appropriate controls and verified during APS.

SUS 的关键人工操作，例如装配和连接，应在 APS 中进行适当的控制和确认。

9. Environmental & process monitoring 环境和工艺监控

General 概述

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.
工厂的环境和工艺监测计划是整体污染控制策略（CCS）的一部分，应用于监测旨在将微生物和颗粒污染风险降至最低的控制措施。应该注意监控系统（活性的、非活性的和 APS）的每一个要素单独使用时的可靠性都是有限的，不应被单独视作无菌的指标。当同时考虑时，这些监测结果将有助于确认所监测的系统在设计、验证和操作方面的可靠性。

9.2. This programme is typically comprised of the following elements:
该监测计划通常由以下几个要素组成：

i. Environmental monitoring – total particle.
环境监测 –总粒子数。

ii. Environmental and personnel monitoring – viable particle.
环境和人员监测 –活性粒子。

iii. Temperature, relative humidity and other specific characteristics.
温度、相对湿度和其他特定的监测项目。

iv. APS (aseptically manufactured product only).
无菌工艺模拟 APS（仅无菌生产的产品）。

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.
来自监测系统的信息应被用于日常批确认/放行以及工艺回顾或调查时的定期评估。这适用于最终灭菌和无菌工艺，但是，影响的关键程度可能因产品和工艺类型而不同。

Environmental and process monitoring 环境和工艺监测

9.4. An environmental monitoring programme should be established and documented. The purpose of the environmental monitoring programme, is to:
应建立书面环境监测计划，其目的是：

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.
确保洁净室或洁净空气设备按照其设计和法规要求持续提供具有适当空气洁净度的环境。

ii. Effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality.
有效监测环境偏离要求的情况，并触发对产品质量风险的调查和评估。

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.
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.
应通过风险评估建立全面的环境监测计划，即采样位置、监测频率、监测方法和培养条件（例如时间、温度、有氧和/或无氧条件）。
风险评估应该基于以下详细知识开展：工艺输入与终产品、设施、设备、特定工艺和步骤的关键性、涉及到的操作、日常监测的数据、确认时获得的监测数据和从环境中分离得到的典型微生物菌群知识。
风险评估应包含确定关键监测位置，生产过程中，这些位置出现的微生物可能会影响产品的质量（例如 A 级区域、无菌生产区域以及 A 级直接连接着的 B 级区域）。还应考虑其他信息，如气流可视化研究。应定期回顾这些风险评估，以确认环境监测计划的有效性。环境监测计划应在趋势分析和工厂 CCS 的整体背景下考虑。

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.
洁净室、洁净空气设备和人员的日常监测应在贯穿所有关键工艺阶段的生产时下进行，包括设备组装。

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).
其他监测项目，例如温度、相对湿度，应该控制在符合产品/工艺/人员相应要求的范围内，并支持所定义的洁净级别标准（例如 A/B 级）。

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 appropriate to obtain reliable data from the critical zones.
A 级的监测应该证明在关键操作过程中无菌生产环境的维持情况，监测应该在对无菌设备表面、容器、密封件和产品造成最高污染风险的位置进行。监测位置、方向以及取样设备的放置位置应该经过评估且合理，以获得关键区域的可靠数据。

9.8. Sampling methods should not pose a risk of contamination to the manufacturing operations.
取样方法不应给生产操作造成污染风险。

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.
应对活性微粒和总粒子数的监测结果设立适当的警戒限和纠偏限。最大总粒子数的行动限参见表 5，最大活性粒子数的行动限参见表 6。但是，基于数据趋势、工艺特性或 CCS 中的规定，可能需要使用更严格的行动限。另外，应根据洁净室级别确认中的测定结果建立活性微粒和总粒子数的警戒限，并根据持续监测的数据趋势进行定期回顾。

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 deterioration of environmental control) are detected and addressed.
应设定 A 级（仅总粒子数）、B 级、C 级和 D 级的警戒限以监测和处理不良趋势（例如多次事件或能指示环境控制效果变坏的个例事件）。

9.11. Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:
监测程序应该定义趋势分析的方法。趋势分析包括但不限于:

i. Increasing numbers of excursions from action limits or alert levels.
超出纠偏限或警戒限次数的持续增加。

ii. Consecutive excursions from alert levels.
连续超出警戒限。

iii. Regular but isolated excursion from action limits that may have a common cause, (e.g. single excursions that always follow planned preventative maintenance).
有规律但孤立的超出行动限可能有共同的原因，例如总是在计划的预防性维护之后出现单次超标。

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.
微生物菌落形态、数量及具有生长优势的特定微生物方面的变化。应特别注意那些表示洁净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。

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.
C 级和 D 级洁净室的动态监测应基于级别确认和日常监测的数据，以便进行有效趋势分析。警戒限和行动限取决于所进行的操作的性质。行动限可能比表 5 和 表 6 中列出的更严格。

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.
如果超出了行动限，操作规程中应描述根本原因调查、对产品潜在影响的评估的要求（包括在监测和报告期间生产的批次）以及纠正和预防措施的要求。如果超过警戒限，操作程序应描述评估和跟踪要求，其中应包括考虑调查和/或采取纠正措施，以避免环境的进一步恶化。

Environmental monitoring – total particle 环境监测—总粒子数

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.
应建立总粒子数监测计划，获取数据用以评估潜在污染风险，确保无菌操作环境维持在经确认的状态。

9.15. The limits for environmental monitoring of airborne particle concentration for each graded area are given in Table 5.
环境监测中，各级别的悬浮粒子浓度监测限度见表 5。

Table 5: Maximum permitted total particle concentration for monitoring.
表 5 总粒子数监测最大允许浓度

Grade 级别	Maximum limits for total particle 最大总粒子限度 ≥ 0.5 μm/m³		Maximum limits for total particle 最大总粒子限度 ≥ 5 μm/m³	
	At rest 静态	In operation 动态	at rest 静态	In operation 动态
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] 非事先规定(a)	29 300	Not predetermined[a] 非事先规定(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.
对于 D 级，动态标准未明确规定。在合适的情况下，企业应基于风险评估和日常监测数据来建立动态下的限度。

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).
注 1：表格中所列“静态”总粒子数的限度值应在操作完成后处于无人状态、经确认期间定义的短暂“自净”后获得（指导值少于 20 分钟），（参见 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.

注 2：由于电子噪声、杂散光、重合损失等情况，A 级区内偶尔出现的大粒子计数，尤其是≥5μm 的大粒子，可能会被看做计数错误。但是，连续地或者有规律地的低水平计数结果可能表明可能存在污染事件，应进行调查。此类事件可能表明洁净室空调系统的早期故障、设备故障，也可能作为设备组装和日常操作期间不良做法的诊断提示。

9.16. For grade A, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.

针对 A 级区，粒子（包括活性粒子和总粒子数，译者注）监测应该在整个关键操作中进行，包括设备组装。

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 (1ft3) 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.

A 级区应采用适当的采样流速（至少 28L/min（1ft3/min））进行持续监测（≥0.5 和≥5μm 的微粒），以捕获所有干扰、瞬态事件以及任何系统损坏的情况。系统应该频繁地将单个结果与警戒限和行动限进行对比，该频率应能发现并及时反馈任何潜在的偏离。如果超过警戒限应触发报警。程序中应规定当报警时应采取何种措施，包括考虑进行额外的微生物监测。

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 deterioration. If alert levels are exceeded, alarms should be triggered.

建议 B 级区使用类似的方式进行监测，但采样频率可能会降低。B 级区应以适当的频率和适当的取样量来进行监测，监测计划应能够监测到任何污染水平的增加和系统恶化。如超过警戒限，应触发报警。

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

监测系统的选择应考虑生产操作中使用的物料（例如可能引起生物/化学/放射性危害的活生物组织、

粉末状产品或者放射性药物）所引入的任何风险。

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.

如果因工艺过程产生污染物，且可能对粒子计数器有潜在损坏或引起危害时（如：活生物组织、粉末状产品和放射性危害），其监测频率和策略应能确保在风险暴露前后的环境级别。应考虑增加微生物监测来确保全面的工艺监控。另外，应在模拟操作期间进行监测。此类操作应该在适当间隔内执行。操作的方法应在 CCS 中进行定义。

9.21. The size of monitoring samples taken 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 cleanrooms and clean air equipment. Monitoring sample volumes should be justified.

使用自动系统进行监测时，采样量通常取决于所用系统的采样速率。采样量不需与洁净室和洁净空气设备在正式级别确认的采样量一致。采样量的设定应该说明理由。

Environmental and personnel monitoring – viable particle 环境和人员监测—活性微粒

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.

无菌操作时，应经常进行微生物监测，使用诸如沉降碟、浮游空气（采样器）、五指手套、洁净服和表面取样(如棉签和接触碟)等组合的方法。所使用的取样方法应该在 CCS 中论证并且应该证明不会对 A/B 级流型产生不利影响。生产操作结束时，应当对洁净室和设备表面进行监测。

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).

洁净区内的活性微粒监测在生产操作未发生时也应该进行，(例如消毒后、开始生产之前、批生产完成时、停产结束后)以及在未使用的相关房间内进行，以检测可能影响洁净区内控制的潜在污染事件。在发生异常情况时，额外的采样点可用于确认纠正措施(例如清洁和消毒)的有效性。

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.

在关键工艺的整个过程中应对 A 级区进行连续空气活性微粒监测（例如浮游菌采样和沉降碟采样），包括设备(无菌组装)组装和关键工艺过程。应基于无菌工艺影响的风险考虑是否在 B 级洁净区使用类似的方式进行监测。监测应能捕获所有干预、瞬时事件和任何的系统恶化，并避免任何由监测操作造成的干扰风险。

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 continuation of activity. Where monitoring of gowns is required after critical interventions, the gown should be replaced before further activity in the cleanroom.

根据员工所执行的活动和与关键区域的接近程度，来对人员监测的位置、类型和频率进行风险评估。监测应包括在工艺操作中以适当时间间隔对人员进行采样。人员采样应以不影响工艺的方式进行。对人员的监测应特别关注，需在参与关键干预后（至少进行取样手套，可能需要对洁净服适当的区域进行取样）以及每次退出 B 级洁净室时（手套和洁净服）进行取样。当在关键干预后进行了手套监测，则应在继续操作之前更换外层手套。如果在关键干预后需要进行洁净服取样监测，则应在下一步活动之前更换洁净服。

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.

应对 A/B 级区的人员进行微生物监测。如果生产操作本质上是手动的（例如无菌配制或灌装），，那么增加的风险应引起对洁净服的微生物监测的加强，并在 CCS 内证明其合理性。

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).
如果日常监测是由生产员工采样，则应在质量部门人员的监视下进行。（参见 8.19）

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.
生产商应考虑采用适宜的替代监测系统（例如快速方法）以加速微生物污染事件的发现，降低对产品的风险。在通过验证证明相对于目前已建立的方法具有等效性或优越性后，这些快速和自动微生物监测方法可以应用。

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.
应充分理解所用的采样方法和设备，并有操作程序指导正确操作进而对所获得结果进行解释。所选采样方法的微生物回收效果应当有数据支持。

9.30. Action limits for viable particle contamination are shown in Table 6
如表 6 所示，活性微粒污染的行动限。

Table 6: Maximum action limits for viable particle contamination
表 6:活性微粒污染的最高行动限

Grade 级别	Air sample cfu/m³ 浮游菌 cfu/m³	Settle plates (diameter 90 mm) cfu/4 hours [a] 沉降菌（直径 90mm）cfu/4小时[a]	Contact plates (diameter 55 mm) cfu/plate[b] 表面微生物（直径 55mm）cfu/皿[b]	Glove print, Including 5 fingers on both hands CFU/ glove 手套接触，包括双手5指手套菌落 CFU/手套
A	No growth [c] 没有生长[c]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

(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).
  沉降碟应该在操作过程中（包括设备组装）暴露在 A/B 级采样，并且在最多四小时后按需更换（暴露时间应基于验证，包含回收率研究，并且不能对所用培养基的适用性有任何不利影响）。

- For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM.
  对于 C/D 级，沉降碟的暴露时间（最多 4h），采样频率应通过质量风险评估确定。

- Individual settle plates may be exposed for less than 4 hours.
  单个沉降碟可能暴露少于 4 小时。

(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.
接触碟限度适用于 A 级和 B 级区内的设备、房间和洁净服表面。根据 C 级和 D 级区域的功能，一般不需要进行 C/D 级洁净服监测。

(c) It should be noted that for grade A, any growth should result in an investigation.
得注意的是，对于 A 级，任何长菌都需要进行调查。

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).
注 1：应该注意上表中所列的监测方法是举例，其他方法也可以使用，只要它们满足在产品可能受到污染的整个关键过程中提供信息的意图（例如无菌线组装、无菌工艺、灌装和冻干上料）。

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.
注 2：整个文件中的限度标准是用 CFU 表示的。如果不同的或新的技术使用不同于 CFU 的其他方式来表达结果，生产商应该科学地说明所用限度的合理性，并且在可能的情况下将其与 CFU 相关联。

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.
如果在 A 级或 B 级区监测到微生物，应将其鉴定到种，并针对这些微生物对产品质量(对每一相关的批次)和总体控制状态的潜在影响进行评估。对 C 级和 D 级区域发现的微生物也应该考虑进行鉴定（例如，超过警戒限或纠偏限），或者对于那些指示洁净度恶化、失控的微生物或者是那些难以控制的例如孢子 –形成微生物和霉菌）以及需要足够的频率以维持对这些区域典型菌落当前的理解时，应考虑进行菌落分离。

Aseptic process simulation (APS) (also known as media fill)
无菌工艺模拟 APS（又名培养基模拟灌装）

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.
对无菌工艺控制的有效性的定期确认，应该包括使用无菌营养培养基和/或替代物来代替由产品进行的 APS。APS 不应被视为验证无菌工艺或无菌工艺各方面的主要方式。无菌工艺的有效性应该通过工艺设计、遵守药品质量体系 PQS 和工艺控制、培训，以及评估监测数据等方式来确定。应该基于培养基和/或替代品模拟产品物理特性的能力来选择适当的营养培养基和/或替代品，产品的物理特性是通过其在无菌工艺过程中对产品无菌性的风险来评价的。若工艺阶段可能会间接影响任何被引入的微生物的活性（例如无菌生产的半固体、粉末、固体物料、微球、脂质体和其它经冷却的或加热的或冻干的剂型），，则应开发能够尽可能代表生产操作的替代程序。如果在 APS 部分工艺中使用替代品，如缓冲液，则替代物料不应抑制任何潜在微生物的生长。

9.33. The APS should imitate as closely as possible the routine aseptic manufacturing process and include

all the critical manufacturing steps, specifically:
APS 应尽可能地模拟日常无菌生产工艺，并包括所有关键的生产步骤。具体如下：

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.
APS 应评估在工艺过程中从物料灭菌、去污染操作之后到容器被密封中间所有的无菌操作。

ii. For non –filterable formulations, any additional aseptic steps should be assessed.
对于不能过滤的剂型，任何额外的无菌步骤都应进行评估。

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.
当无菌操作在惰性气体中进行时，APS 中应该使用空气代替惰性气体除非目的是模拟厌氧环境。

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.
需要添加无菌粉末的工艺应该采用一种可接受的替代品，该替代品应装在与被评估的工艺中所使用的相同容器中。

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.
应避免分别对独立单元操作（如涉及无菌粉末的干燥、混合、磨粉、分装过程）进行模拟。任何单独模拟都应该有书面的理由支持并保证所有单独模拟在总体上能持续、全面地覆盖整个工艺。

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.
冻干产品的 APS 程序应代表整个无菌操作链，包括灌装、转运、装载、具有代表性的腔体保压时长、卸载和密封，并在特定的、被记录的、合理的、能代表最差条件的参数下进行。

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:

冻干工艺模拟应该模拟所有无菌工艺，除非会影响污染物的活性或回收率。例如，应避免沸腾或溶液的实际冻干。适当时，APS 设计时应考虑的因素包括：

- The use of air to break vacuum instead of nitrogen or other process gases.
  使用空气代替氮气或其他工艺气体来破真空。

- Replicating the maximum interval between sterilisation of the lyophilizer and its use.
  重现冻干机除菌到使用时的最大间隔。

- Replicating the maximum period of time between filtration and lyophilization.
  重现（产品）过滤到冻干的最长时间间隔。

- 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.
  量化最差条件，如装载最大数量的托盘、重现腔室开放在环境中的最长的装载时间。

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:
APS 应考虑在正常生产过程中以及最差的情况下会发生的各种无菌操作和固有干预，考虑以下内容：

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.
常规工艺中固有和纠正干预的开展方式和频率应该和常规无菌工艺类似。

ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility.
APS 中的干预内容和频率应基于对产品无菌性的风险来确定。

9.35. APS should not be used to justify practices that pose unnecessary contamination risks.
APS 不应被用来论证那些引入非必要污染风险的操作。

9.36. In developing the APS plan, consideration should be given to the following:
在制定 APS 计划时，应考虑以下内容：

i. Identification of worst case conditions covering the 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.
识别最差的情况，包括相关变量，例如容器大小和生产线速度，及其对工艺的影响。评估的结果应

该为所选择的变量提供合理说明。

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.
确定用于验证的容器/密封件组合的代表性尺寸。在证明不同产品、相同容器/密封件工等效性的情况下，可以考虑用括号法或矩阵法对相同的容器/密封组合进行验证。

iii. Maximum permitted holding times for sterile product and equipment exposed during the aseptic process.
无菌产品和设备在无菌工艺中允许的最长保存时间。

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.
每个容器灌装的体积，应该足以确保培养基接触到所有可能直接污染无菌产品的设备和部件表面。应该有充足的顶部空间以支持潜在的微生物生长，并且确保能在检查期间发现浑浊。

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).
除厌氧模拟外，应用空气替代日常无菌生产过程中使用的惰性气体。这些情况下，应考虑将偶尔进行厌氧模拟作为整体验证策略的一部分(参见第 9.33 段 iii)。

vi. The selected nutrient media should be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates.
所选择的培养基应该能支持相关药典中指定菌种和适宜的代表性本地分离菌的生长。

vii. The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.
微生物污染物的检查方法应该被科学地证明，以确保任何污染物都能可靠地被检测到。

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.

APS 应有充足的时间来挑战工艺、进行干预的人、换班以及为无菌产品生产提供合适条件的工艺环境的能力。

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.
当生产商采用倒班或者长时间班次时，APS 的设计应该能捕获那些与班次相关并对产品无菌性有风险的因素，例如操作员在洁净室工作的最长时间。

x. Simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment).
在生产空闲时模拟正常无菌生产时的中断（例如换班、分装料斗补料、引入额外设备）。

xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.
确保环境监控按照日常生产要求进行，并且贯穿整个 APS.

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.
当阶段性生产时，例如使用屏障技术或生产无菌活性物质，在设计和执行 APS 时应考虑需要模拟阶段性生产开始和结束时的风险，证明阶段性生产时长不会带来任何风险。

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.
“生产结束或阶段性生产结束执行的 APS”可能用作额外的保证或调查目的；但是，它的使用应在 CCS 中说明，并且不应该代替常规的 APS。如果应用，应证明任何残留的产品不会对任何潜在微生物污染的回收造成负面影响。

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.

对于无菌活性物质，批量大小应足以代表日常生产，模拟在最差的情况下的干扰操作，并覆盖可能与无菌产品有接触的所有表面。此外，所有被模拟的物质(替代物或生长媒介)都应进行微生物的评估。模拟物料应充足以满足被模拟工艺的评估，且不应损害微生物的回收。

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 performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.

APS 应该作为初始验证的一部分，应有至少三次连续的满足要求的模拟测试，并涵盖所有工作班次，以及当操作规范、设施、服务或设备发生了被评估为对产品无菌保障有影响的重大变动后（例如 HVAC 系统改造、设备、工艺变动、班次数和人员数量、主要设施关停）。对于每一种无菌工艺、每条灌装线和每个班次，APS(周期性再验证)通常一年应该被重复两次(大约每六个月一次)。每名操作人员至少要每年参加一次成功的 APS。当生产线停产前、长期不使用、或者在停用或移位前，应该在最后一个生产批次后进行一次无菌工艺模拟试验。

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.

当手动操作时（如无菌配制或分装），，每种类型的容器/密封件和设备系列应该先经过验证，每个操作人应该参与至少三次连续成功的 APS，并且每班大约每 6 个月再进行一次 APS。APS 批量大小应模拟常规的无菌生产工艺。

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.

(灌装)工艺模拟试验单元的数量应足以有效模拟代表无菌生产过程的所有活动;应该 CCS 中清楚地确定需要灌装的单元数量的理由。通常，最少灌装 5000 –10000 个单位。对于小批量的，例如那些少

于 5000 个单元的，培养基灌装的容器的数量应该至少等于生产批次的数量.

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 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.
装后的 APS 容器在培养前应摇动、旋转或倒置，以确保培养基与容器内所有内部表面接触。APS 中所有完整的容器都应该进行培养并评估，包括有外观缺陷的容器，以及经历过非破坏性中控检查的容器。在 APS 中被剔除的容器和不进行培养的容器应该与在常规灌装过程中剔除的容器相同，且只有当生产 SOP 中明确规定在相同情况下（即干扰类型、生产线位置、移除的容器的具体数量）才可以移除容器。在任何情况下，APS 干预中移除的容器都不应该多于常规生产中剔废的容器。例如常规生产中组装后或特定干预类型后那些必须剔废的容器。为了充分理解工艺以及评估无菌组装或强制清理生产线期间的污染风险，这些容器通常会单独进行培养，不一定要包含在 APS 的可接受标准中。

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.
如果工艺过程中有物料与产品表面接触，但随后被废弃（例如产品冲洗），则在 APS 中应使用培养基模拟丢弃的物料，并将其培养，除非能够清楚地证明该废弃过程不会影响产品的无菌性。

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.
灌装后的 APS 样品应该在一个透明的容器中培养，以确保微生物生长的目视检查。如果产品容器不透明(如琥珀色玻璃、不透明塑料)，可以用相同材质的透明容器代替，以助于污染检测。当不能使用

相同材质的透明容器替代时，应开发并验证一种合适的检测微生物生长的方法。从受污染的容器中分离出来的微生物应被鉴定到种，以协助确定污染的可能来源。

9.44. Filled APS units should be incubated without unnecessary 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.
灌装后 APS 容器应该尽快培养，避免非必要的延迟，以确保达到潜在污染物的最高的回收率。所选择的培养条件和周期应该经过科学论证并验证，以提供适当的微生物检测灵敏度水平。

9.45. On completion of incubation:
培养结束后：

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.
灌装的 APS 容器应由经过适当培训并具备微生物污染检查资格的人员在有利于识别出微生物污染的条件下进行检查。

ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.
灌装的样品应通过接种适当范围的标准菌和具有适当代表性的本地分离菌进行阳性对照试验。

9.46. The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken:
目标应该是零生长，任何受污染的容器都应判定 APS 失败，并应采取以下行动:

i. An investigation to determine the most probable root cause(s).
调查最可能的根本原因。

ii. Determination and implementation of appropriate corrective measures.
确定并实施适当的纠正措施。

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.
应进行足够数量的成功的连续重复 APS(通常至少 3 次)，以证明该过程已恢复到受控状态。

iv. A prompt review of all appropriate records relating to aseptic production since the last successful

APS.
迅速回顾自上次 APS 成功以来有关无菌生产的所有相关记录。

a) The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS.
回顾的结果应包括对自上次成功的 APS 以来生产的批次中潜在无菌阳性的风险评估。

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.
所有未上市的批次都应纳入调查范围。任何有关其放行状态的决定都应考虑调查结果。

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.
在 APS 失败后，所有在生产线上生产的产品都应该隔离，直到问题被成功解决。

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.
若根本原因调查表明 APS 失败与操作人员的行为相关，则应采取措施限制该操作人员的行为，直到经过重新培训和资质确认。

vii. Production should resume only after completion of successful revalidation.
只有在重新验证成功后才能恢复生产。

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.
所有的 APS 都应该被完整的记录下来，包括对被处理的容器的数量核对(如灌装的、培养的，未培养的)。对灌装的和未培养的容器的理由应包括在文件中。应当记录在 APS 期间执行的所有干预，包括每次干预的开始和结束时间以及相应的人员。所有微生物监测数据和其他检测数据应记录在 APS 批记录中。

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.
只有当书面程序中规定了商业批次需要同样处理的情况下，APS 运行才可以被中止。这种情况下，应该记录调查情况。

9.49. An aseptic process should be subject to a repeat of the initial validation when:
在以下情况下，无菌工艺应重新进行首次验证:

i. The specific aseptic process has not been in operation for an extended period of time.
特定的无菌生产工艺已经很长时间没有生产了。

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.
工艺、设备、程序或环境的变化有可能潜在影响无菌工艺，或采用新的产品容器或密封件组合。

10. Quality Control （QC） 质量控制（QC）

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.
应配备在微生物学、无菌保障和工艺知识方面有适当和经验的人员，以支持生产活动、环境监测计划的设计以及任何微生物事件相关联无菌产品安全性影响的调查评估。

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.
当监测和/或 CCS（污染控制策略）需要时，原料、组分和产品的质量标准应包含微生物、 微粒和内毒素/热源限度的要求。

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.
对于无菌灌装产品和最终灭菌产品，应对每批产品进行微生物负荷测定，其结果应作为最终批审核的一部分。应定义在终端除菌级滤器或终端灭菌步骤之前的生物负荷标准，此标准与所使用方法的效率有关。应在能代表最差条件的情况 (例如在保存时间结束时)进行取样。如果为最终灭菌产品设置过度灭菌参数时，则应在适当的预定时间间隔监测生物负荷。

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.
对于被批准进行参数放行的产品，在灭菌开始循环之前，应为已灌装产品制定支持性灭菌前生物负荷监测计划，并对每个批次产品都要进行生物负荷测定。灭菌前灌装单位的取样位置应基于最差 的情况（确定），并具有代表性。应在生物负荷测定期间发现的任何微生物都应鉴定，并确定其对灭菌工艺有效性的影响。如有必要，应监测内毒素/热原水平。

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.
成品无菌检测，只能作为无菌保证一系列关键控制措施中的最后一项。它不能用于确 保不符合其设计、程序或验证参数的产品的无菌性。应对相关产品的无菌检测进行验证。

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:
无菌检测应在无菌条件下进行。用于无菌检测的样品应能够代表整个批次，但应特别包括从被认为最有可能受到污染的部分采集样品,例如:

i. For products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch. Additional samples, e.g. taken after critical interventions should be considered based on risk.
对于无菌灌装的产品，样品应包括在批次开始和结束时灌装的容器。应基于风 险考虑其他样品，如在关键干预措施后进行取样。

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).
对于在最终容器中进行热力灭菌的产品，所取的样品应能代表最差情况的位置（例如，每个装载中可能最冷点或加热最慢的部分）。

iii. For products which have been lyophilized, samples taken from different lyophilization loads.
对于冻干的产品，从不同的冻干装载中取样。

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.
注: 如果生产过程中有含亚批 (例如， 最终灭菌的产品)，则应从每亚批中进行无菌样品的取样， 并对每亚批进行无菌检测。还应该考虑对其他成品检测项目进行单独测试。

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.

对于某些产品，由于产品的有效期太短，无菌检测可能无法在放行前完成并获得无菌检测结果。在这种情况下，应评估和记录降低已识别风险所需的工艺设计以及额外监测和/或替代测试方法的额外考虑。

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.

在检测前，用于对无菌样品外表面进行去污染（清洁消毒）的任何过程（如 VHP、紫外线）都不应对检测方法的灵敏度或样品的可靠性产生负面影响。

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.

用于产品检验的培养基在使用前应根据相关药典进行质量控制测试。用于环境监测和 APS 的培养基应在使用前使用科学合理并经指定的参考菌株和包含适合代表本地的分离株进行促生长试验。培养基质量控制测试通常由终端用户进行。任何依托培养基外包测试或供应商测试的都应经过论证，并应全面考虑在此情况下的运输条件。

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 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.

洁净区产生的环境监测数据和趋势数据应作为产品批放行的一部分进行审核。应提供书面程序说明当发现环境监测数据超趋势或超过规定限度时应采取的行动。对于有效期短的产品，可能无法获得生产时的环境监测数据；在这些情况下，应包括对最近可用数据的审核，这些产品的生产商应考虑使用快速/替代方法。

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.

如果快速和自动化微生物方法用于一般生产目的，则应针对相关产品或工艺使用这些方法进行验证。

Glossary 术语

Airlock – An enclosed space with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an airlock is to preclude ingress of particle matter and microorganism contamination from a lesser controlled area.
气锁（气闸）—指带有互锁门的密闭空间，用于维持相邻房间（通常是具有不同的空气洁净度标准）之间的气压控制。气锁的目的是为了防止从较低控制级别区域引入颗粒物质和微生物污染。

Action limit – An established relevant measure (e.g. microbial, or airborne particle limits) that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.
行动限—指设定的相关衡量指标（例如微生物或空气中悬浮粒子限度），当超出时，应进行适当的调查并根据调查情况采取纠正措施。

Alert level – An established relevant measure (e.g. microbial, or airborne particle levels) giving early warning of potential drift from normal operating conditions and validated state, which does not necessarily give grounds for corrective action but triggers appropriate scrutiny and follow –up to address the potential problem. Alert levels are established based on routine and qualification trend data and are periodically reviewed. The alert level can be based on a number of parameters including adverse trends, individual excursions above a set limit and repeat events.
警戒限—指设定的相关衡量指标（例如：微生物或者空气中悬浮粒子水平），可以为潜在偏离常规操作条件和验证状态的情况提供早期预警，这不一定需要采取纠正措施，但应进行适当的监控和跟踪以解决潜在问题。警戒级别应该基于日常监测数据和确认趋势数据的建立的，并定期进行回顾。警戒限可以基于多个参数，包括不良趋势、超出设置限度的单个偏离事件，以及重复事件。

Aseptic preparation/processing – 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, endotoxin/pyrogen and particle contamination.
无菌准备/处理—在受控环境中处理无菌产品、容器和/或设施，在此环境中，送风、物料和人员都加以管控以防止微生物、内毒素/热原和粒子的污染。

Aseptic Process Simulation (APS) – A simulation of the entire aseptic manufacturing process in order to verify the capability of the process to assure product sterility. Includes all aseptic operations associated with routine manufacturing, e.g. equipment assembly, formulation, filling, lyophilization and sealing processes as necessary.
无菌工艺模拟（APS）—对整个无菌生产工艺的模拟，以确认工艺有能力保障产品的无菌性。包括所有与常规生产相关的无菌操作，例如，必要时进行设备组装、配料、灌装、冻干和密封操作。

Asepsis – A state of control attained by using an aseptic work area and performing activities in a manner

that precludes microbial contamination of the exposed sterile product.
无菌——通过使用无菌工作区域并以防止暴露的无菌产品被微生物污染的方式来执行活动的一种控制状态。

Bacterial retention testing – This test is performed to validate that a filter can remove bacteria from a gas or liquid. The test is usually performed using a standard organism, such as Brevundimonas diminuta at a minimum concentration of 10^7 Colony Forming Units/cm^2.
细菌截留测试：执行此实验是为了验证过滤器可以去除气体或者液体中的细菌。通常使用一种标准菌株进行实验，例如最低浓度为 10^7CFU/cm^2 的缺陷短波单孢菌。

Barrier – A physical partition that affords aseptic processing area (usually grade A) protection by separating it from the background environment. Such systems frequently use in part or totally the Barrier Technologies known as RABS or isolators.
屏障— 一种物理分区系统，将无菌操作区域（通常为 A 级）与背景环境分开来提供无菌操作环境的保护。这样的系统经常部分或全部使用被称为 RABS 或隔离器的屏障技术。

Bioburden – The total number of microorganisms associated with a specific item such as personnel, manufacturing environments (air and surfaces), equipment, product packaging, raw materials (including water), in –process materials, or finished products.
生物负载—与特定项目相关的微生物总数，包括人员、生产环境（空气和表面）、设备、产 品包装、物料（包括水）、中间产品或成品。

Bio –decontamination – A process that eliminates viable bioburden via use of sporicidal chemical agents.
生物净化—通过使用化学杀孢子剂消除活性微生物负载的一种工艺。

Biological Indicators (BI) – A population of microorganisms inoculated onto a suitable medium (e.g. solution, container or closure) and placed within a steriliser or load or room locations to determine the sterilisation or disinfection cycle efficacy of a physical or chemical process. The challenge microorganism is selected and validated based upon its resistance to the given process. Incoming lot D –value, microbiological count and purity define the quality of the BI.
生物指示剂（BI）—将微生物接种到合适的介质（例如溶液、容器或封闭物）上并置于灭菌器或房间中的装载位置以确定物理或化学灭菌或消毒工艺的效果。挑战用微生物的选择和验证应基于其对特定灭菌工艺的耐受能力。购进批的 D 值、微生物数量和纯度决定了 BI 的质量。

Blow –Fill –Seal (BFS) – A technology in which containers are formed from a thermoplastic granulate, filled with product, and then sealed in a continuous, integrated, automatic operation. The two most common types of BFS machines are the Shuttle type (with Parison cut) and the Rotary type (Closed Parison).
吹灌封技术（BFS）— 一种技术，其容器由热塑颗粒制成，在灌装产品后通过连续、集成、自动化的操作进行密封。最常见的两种 BFS 机器类型是梭式（带有型坯切割）和旋转式机器 （封闭型坯）。

Campaign manufacture – A manufacture of a series of batches of the same product in sequence in a given period of time with strict adherence to established and validated control measures.
连续生产—在给定的时间段内，按顺序生产一系列批次的相同产品，并严格遵守既定且经过验证的控制措施。

Classified area – An area that contains a number of cleanrooms (see cleanroom definition).
分级区域—包含多个洁净室的一个区域（参见洁净室定义）。

Cleaning – A process for removing contamination e.g. product residues or disinfectant residues.
清洁— 一种清除污染物的工艺，例如产品残留物和消毒剂残留物。

Clean area – An area with defined particle and microbiological cleanliness standards usually containing a number of joined cleanrooms.
洁净区— 指具有明确粒子和微生物洁净度标准的区域，通常包含多个相连的洁净室。

Cleanroom – A room designed, maintained, and controlled to prevent particle and microbial contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness level.
洁净室— 指经过设计、维护和控制以防止药品被粒子和微生物污染的房间。这样的房间被指定并可持续地满足适当的空气洁净度水平。

Cleanroom classification – 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.
洁净室分级—一种通过测量总粒子浓度，根据洁净室或洁净空气设备规范评估空气洁净度水平的方法。

Cleanroom qualification – A method of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use.
洁净室确认—一种评估分类洁净室或洁净空气设备是否符合其预期用途的方法。

Closed system – A system in which the product is not exposed to the surrounding environment. For example, this can be achieved by the use of bulk product holders (such as tanks or bags) that are connected to each other by pipes or tubes as a system, and where used for sterile products, the full system is sterilised after the connections are made. Examples of these can be (but are not limited to) large scale reusable systems, such as those seen in active substance manufacturing, or disposable bag and manifold systems, such as those seen in the manufacture of biological products. Closed systems are not opened until the conclusion of an operation. The use of the term “closed systems” in this Annex does not refer to systems such as RABS or isolator systems.
密闭系统—使产品不暴露于周围环境的系统。例如，可以通过使用管道或软管相互连接的待分装/灌装产品

支架（例如罐子或袋子）作为一个系统来实现，并且在用于无菌产品的情况下，整个系统连接后进行消毒灭菌被制作。这些系统可以是（但不限于）大规模重复使用的，例如在活性成分生产中的系统，或一次性袋子和歧路系统，例如在生物产品生产中的系统。在操作结束之前，密闭系统不应被打开。本附录中使用的术语“密闭系统”，不包括 RABS 或隔离器系统。

Colony Forming Unit (CFU) – A microbiological term that describes a single detectable colony that originates from one or more microorganisms. Colony forming units are typically expressed as CFU per ml for liquid samples, CFU per m3 for air sample and CFU per sample for samples captured on solid medium such as settle or contact plates.

菌落形成单位（CFU）—微生物学术语，指源自一个或者多个微生物形成的单个可检测菌落。对于液体样品，菌落形成单位通常表示为 CFU/ml，对于空气样品表示为 CFU/m³， 对于在固体介质（如沉降或接触碟上）采集的样品，菌落形成单位通常表示为 CFU/样品。

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

污染— 生产、取样、包装或重新包装、存储或运输过程中，具有微生物性质的杂质（微生物的数量和类型，热原）或外来粒子被意外地引入到物料、中间产品、活性物质或制剂产品中， 并可能会对产品质量产生不利影响。

Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in – process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

污染控制策略（CCS）—从对当前产品和工艺的理解中得出的一套有计划的针对微生物，热原和粒子的控制措施，以确保工艺性能和产品质量。控制措施可以包括与活性物质、辅料、药品材料和组分、设施和设备的操作条件、过程控制、成品标准以及相关的监控方法和频率有关的参数和属性。

Corrective intervention – An intervention that is performed to correct or adjust an aseptic process during its execution. These may not occur at a set frequency in the routine aseptic process. Examples include such as clearing component jams, stopping leaks, adjusting sensors, and replacing equipment components.

纠正性干预— 在执行过程中纠正或调整无菌过程的一种干预措施。这些措施可能不会在常规的无菌过程中以设定的频率发生。示例包括：清除组件阻塞，阻止泄漏，调整传感器和更换设备组件。

Critical surfaces – Surfaces that may come directly into contact with, or directly affect, a sterile product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.
关键表面—可能与无菌产品或其容器或密闭系统直接接触或产生直接影响的表面。关键表面在生产操作开始之前应达到无菌，并且在整个生产过程中保持无菌性。

Critical zone – A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.
关键区域— 无菌操作区域内，产品和关键表面暴露于环境中的位置。

Critical intervention – An intervention (corrective or inherent) into the critical zone.
关键干预— 对关键区域的干预（纠正或固有）。

D –value – The value of a parameter of sterilisation (duration or absorbed dose) required to reduce the number of viable organisms to 10 per cent of the original number.
D 值—将存活微生物数量减少到原始数量的 10%所需的灭菌参数值（持续时间或吸收剂量）。

Dead leg – Length of non –circulating pipe (where fluid may remain static) that is greater than 3 internal pipe diameters.
死角— 大于 3 倍管道内径的非循环管道（流体可能保持静止）的长度。

Decommission – When a process, equipment or cleanroom are closed and they will not be used again.
停用— 工艺、设备或洁净室关闭且不再使用时。

Decontamination – The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganisms) from an area, object, or person. The method of decontamination used (e.g. cleaning, disinfection, sterilisation) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated. See also Bio –decontamination.
除污染— 从一个区域、物品或人员身上去除或减少任何污染物（化学物质，废物，残留物或微生物）的整个过程。使用的除污染方法（例如清洁、消毒、灭菌）应进行筛选和验证，以达到适合于除污染的预期目的和清洁水平。参见生物除污染。

Depyrogenation – A process designed to remove or inactivate pyrogenic material (e.g. endotoxin) to a specified minimum quantity.
除热原— 旨在将热原物质（例如内毒素）去除或灭活到指定的最小量的过程。

Disinfection – The process by which the reduction of the number of microorganisms is achieved by the irreversible action of a product on their structure or metabolism, to a level deemed to be appropriate for a

defined purpose.
消毒— 通过一种消毒产品对微生物结构或新陈代谢的不可逆作用，将微生物数量减少到被认为符合预期水平的工艺。

Endotoxin – A pyrogenic product (i.e. lipopolysaccharide) present in the Gram negative bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.
内毒素— 存在于革兰氏阴性细菌细胞壁中的热原产物（即脂多糖）。内毒素可导致接受注射的患者发烧甚至死亡的反应。

Equilibration time – Period which elapses between the attainment of the sterilisation temperature at the reference measurement point and the attainment of the sterilisation temperature at all points within the load.
平衡时间— 在参考测量点达到灭菌温度和负载内所有点达到灭菌温度之间所需的时间。

Extractables – Chemical entities that migrate from the surface of the process equipment, exposed to an appropriate solvent at extreme conditions, into the product or material being processed.
可提取物—工艺设备在极端条件下暴露于适当的溶剂中，从工艺设备表面迁移到要加工的产品或物料中的化学物质。

First Air – Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.
初始气流— 指在到达关键区域前，已通过过滤器的、在接触暴露产品或产品接触表面之前未被干扰可能引入污染的气流。

Filter Integrity test – A test to confirm that a filter (product, gas or HVAC filter) retain their retentive properties and have not been damaged during handling, installation or processing.
过滤器完整性测试— 用于确认过滤器（产品、气体或空调系统过滤器）保持其截留性能，在处理、安装、加工过程中未被破坏的一种测试。

Form –Fill –Seal (FFS) –An automated filling process, typically used for terminally sterilised products, which constructs the primary container out of a continuous flat roll of packaging film while simultaneously filling the formed container with product and sealing the filled containers in a continuous process. FFS processes may utilize a single web system (where a single flat roll of film is wrapped around itself to form a cavity), or a dual web system (where two flat rolls of film are brought together to form a cavity), often with the aid of vacuum moulds or pressurised gases. The formed cavity is filled, sealed and cut into sections. Films typically consist of a polymeric material, polymeric coated foil or other suitable material.
成型 –灌装 –密封(FFS)— 一种自动灌装工艺，通常用于最终灭菌的产品，该工艺使用连续平卷的包装薄膜来生产内包装容器，同时向生产成型的内包装容器中灌装产品，并将灌装完成的容器进行密封，整个工艺

都是连续的。FFS 工艺可以使用单网系统（即一个平卷薄膜包裹其自身以形成空腔）或 双网系统（即两个平卷薄膜聚集在一起以形成空腔），通常需要借助真空模具或加压气体。 空腔形成后，向其中灌装、将其密封，然后切割成单个包装。薄膜通常由聚合物材料、聚合物涂层箔或其他合适的材料组成。

Gowning qualification – A programme that establishes, both initially and on a periodic basis, the capability of an individual to don the complete gown.
更衣确认—确定人员能够完整穿戴无菌服能力的程序，需要首次和定期确认。

Grade A air supply – Air which is passed through a filter qualified as capable of producing grade A total particle quality air, but where there is no requirement to perform continuous total particle monitoring or meet grade A viable monitoring limits. Specifically used for the protection of fully stoppered vials where the cap has not yet been crimped.
A 级送风— 通过了过滤器的空气，该过滤器能够产生符合 A 级总粒子数要求的空气，但不要求执行连续总粒子数监测或满足 A 级微生物的监测限度。专门用于保护没有轧盖的全压塞小瓶。

HEPA filter – High efficiency particulate air filter specified in accordance with a relevant international standard.
HEPA 过滤器—依据相关国际标准规定的高效粒子空气过滤器。

Inherent interventions – An intervention that is an integral part of the aseptic process and is required for either set –up, routine operation and/or monitoring (e.g. aseptic assembly, container replenishment, environmental sampling). Inherent interventions are required by procedure or work instruction for the execution of the aseptic process.
固有干预—是无菌工艺不可或缺的一部分。是组装，常规操作和/或监控（例如：无菌 组装，容器补充，环境取样等）所必需的干预。固有干预措施应遵循规程或作业指导书的要求来执行无菌操作。

Intrinsic sterile connection device – A device that reduces the risk of contamination during the connection process; these can be mechanical or fusion sealing.
固有无菌连接装置—在连接过程中降低污染风险的装置；这些可以是机械密封或熔封装置。

Isokinetic sampling head – A sampling head designed to disturb the air as little as possible so that the same particles go into the nozzle as would have passed the area if the nozzle had not been there (i.e. the sampling condition in which the mean velocity of the air entering the sample probe inlet is nearly the same (± 20 percent) as the mean velocity of the airflow at that location).
等动力取样头—几乎不会对空气产生干扰的取样头，可以使悬浮粒子就像没有经过取样头一样进入取样口。（即进入采样口的空气的平均速度与该位置的气流的平均速度几乎相同（± 20%）。

Isolator – An enclosure capable of being subject to reproducible interior bio –decontamination, with an

internal work zone meeting grade A conditions that provides uncompromised, continuous isolation of its interior from the external environment (e.g. surrounding cleanroom air and personnel). There are two major types of isolators:

隔离器— 能够进行可重复的内部生物净化的外壳，其内部工作区域满足 A 级条件， 可将其内部与外部环境（例如周围洁净室空气和人员）无间断的持续隔离。隔离器主要有两种类型：

i. Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.
密闭式隔离系统通过与辅助设备无菌连接实现物料的转移，而不是使用向周围环境开口的方式，从而隔绝了隔离器内部被外部污染。密闭系统在整个操作过程中保持密封状态。

ii. Open isolator systems are designed to allow for the continuous or semi –continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator.
开放式隔离系统允许在操作期间通过一个或多个开口连续或半连续地传进和/或传出物料。开口经过设计（例如，使用持续正压）以防止外部污染物进入到隔离器。

Leachables – Chemical entities that migrate into products from the product contact surface of the process equipment or containers under normal condition of use and/or storage.
浸出物— 在正常使用和/或存储条件下，从工艺设备或容器的产品接触表面迁移到产品中的化学物质。

Local isolates – Suitably representative microorganisms of the site that are frequently recovered through environmental monitoring within the classified zone/areas especially grade A and B areas, personnel monitoring or positive sterility test results.
本地分离菌— 工厂的代表性微生物，经常在洁净区环境监测（特别是 A 级区域和 B 级区域）、 人员监测或无菌测试结果阳性等途径得到。

Lyophilization – A physical –chemical drying process designed to remove solvents, by way of sublimation, from both aqueous and non –aqueous systems, primarily to achieve product or material stability. Lyophilization is synonymous to the term freeze –drying.
冻干— 通过升华的方式来去除水溶液和非水溶液系统中溶剂的物理 –化学干燥过程，主要是为了实现产品或物料的稳定性。“冻干”与术语“冷冻干燥”是同义的。

Manual aseptic processing– An aseptic process where the operator manually compounds, fills, places and /or seals an open container with sterile product.
手动无菌加工—操作人员手动配制、灌装、放置和/或密封装有无菌产品的开口容器的一种无菌工艺。

Operator – Any individual participating in the processing operation, including line set –up, filling, maintenance, or other personnel associated with manufacturing activities.
操作员— 参与工艺操作的任何个人，包括生产线组装，灌装，维护或与生产活动相关的其他人员。

Overkill sterilisation – A process that is sufficient to provide at least a 12 log10 reduction of microorganisms having a minimum D –value of 1 minute.
过度杀灭— 足以提供使最小 D 值为 1 分钟的微生物至少下降 12 个对数值的一种工艺。

Parison – The "tube" of polymer extruded by the BFS machine from which containers are formed.
型坯— 由 BFS 机器挤出的聚合物“管”，用于形成容器。

Pass –through hatch – Synonymous with airlock (see airlock definition) but typically smaller in size.
传递窗— 与气锁（参考气锁定义）同义，但通常尺寸较小。

Patient – Human or animal including participants in a clinical trial.
患者—人或动物，包括临床试验的参与者

Post –aseptic processing terminal heat treatment– A terminal moist heat process employed after aseptic processing which has been demonstrated to provide a sterility assurance level (SAL) ≤10 –6 but where the requirements of steam sterilisation (for example, F0≥8 min) are not fulfilled. This may also be beneficial in the destruction of viruses that may not be removed through filtration.
无菌加工后终端热处理——无菌加工后使用的一种终端湿热工艺，已证明可提供≤10 –6 无菌保证水平(SAL)。但不符合蒸汽灭菌的要求（例如 F0≥8 分钟）。这也有助于灭活可能无法通过过滤去除的病毒。

Pyrogen – A substance that induces a febrile reaction in patients receiving injections;
热原—可以引起被注射患者的身体发热反应的物质。

Rapid Transfer System/Port (RTP) – A System used for the transfer of items into RABS or isolators that minimizes the risk to the critical zone. An example would be a rapid transfer container with an alpha/beta port.
快速传输系统/端口（RTP）–用于将物品传输到 RABS 或隔离器中的系统，可将关键区域的风险降至最低。例如，具有 α / β 端口的快速传输容器。

Raw material – Any ingredient intended for use in the manufacture of a sterile product, including those that may not appear in the final drug product.
原材料— 用于无菌产品生产的任何成分，包括那些可能不会出现在最终药品中的成分。

Restricted Access Barrier System (RABS) – System that provides an enclosed, but not fully sealed,

environment meeting defined air quality conditions (for aseptic processing grade A), and using a rigid –wall enclosure and integrated gloves to separate its interior from the surrounding cleanroom environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, RTPs and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely opened, and only under strictly pre –defined conditions.

限制进入屏障系统（RABS）— 提供一个封闭但未密封环境的系统，该环境通过使用硬质围挡 和整合在系统上的手套将内部环境与周围环境分开以满足特定的空气质量条件（用于 A 级无菌工艺。RABS 的内表面应经过杀孢子剂消毒和净化。操作员使用手套、半身服、快速传 输系统 RTP 和其他集成的传输端口来执行操作或将材料传输到 RABS 内部。根据设计的不同，门几乎不被打开，或只在严格规定的情况下才能打开。

Single Use Systems (SUS) – Systems in which product contact components are used only once to replace reusable equipment such as stainless steel transfer lines or bulk containers. SUS covered in this document are those that are used in manufacturing processes of sterile products and are typically made up of disposable components such as bags, filters, tubing, connectors, storage bottles and sensors.

一次性使用系统（SUS）—产品接触部件仅使用一次以替代可重复使用的设备（如不锈钢输送管道或大容器）的系统。本文中涉及的 SUS 是指用于无菌产品的生产过程中的那些， 通常由一次性组件组成，例如一次性的袋子、过滤器、管道、连接器、储存瓶和传感器等。

Sporicidal agent – An agent that destroys bacterial and fungal spores when used in sufficient concentration for specified contact time. It is expected to kill all vegetative microorganisms.

杀孢子剂—当在规定的接触时间内以足够的浓度使用时，可以破坏细菌和真菌孢子的药剂。 预计会杀死所有无性繁殖微生物。

Sterile Product – For purpose of this guidance, sterile product refers to one or more of the sterilised elements exposed to aseptic conditions and ultimately making up the sterile active substance or finished sterile product. These elements include the containers, closures, and components of the finished drug product. Or, a product that is rendered sterile by a terminal sterilisation process.

无菌产品— 就本指南而言，无菌产品是指一种或多种暴露在无菌条件下的被灭菌的要素，并最终构成无菌活性物质或无菌产品。这些要素包括容器、密闭物和成品药的组件。或者，通过最终灭菌过程达到无菌的产品。

Sterilising grade filter – A filter that, when appropriately validated, will remove a defined microbial challenge from a fluid or gas producing a sterile effluent. Usually such filters have a pore size equal or less than 0.22 µm.

除菌级过滤器—经过适当验证，可以从流体或气体中去除特定的挑战用微生物，并得到无菌流出物的过滤器。通常，此类过滤器孔径等于或小于 0.22µm。

Terminal Sterilisation – The application of a lethal sterilising agent or conditions to a product in its final container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (e.g. the theoretical probability of there being a single viable microorganism present on or in a sterilised unit is equal to or less than 1 x 10 –6 (one in a million)).
终端灭菌— 在最终容器内的成品使用杀菌剂或特定条件以实现 10^{-6} 或更好的预期无菌保证水平（SAL）。（例如，单个无菌产品中微生物存活的理论概率等于或小于 1×10^{-6}（百万分之一））。

Turbulent airflow – Air that is not unidirectional. Turbulent air in cleanrooms should flush the cleanroom via mixed flow dilution and ensure maintenance of acceptable air quality.
湍流——非单向空气流。洁净室中的湍流空气应通过混流稀释来冲洗洁净室，并确保维持可接受的空气质量。

Unidirectional airflow – An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particles away from the critical processing or testing area.
单向流——以一种稳定而均匀的方式，并以足够的速度向单一方向流动的气流，以便不断地将颗粒从关键的操作区或检验区域中清除。

Unidirectional Airflow (UDAF) unit – A cabinet supplied with filtered unidirectional airflow (previously referred to as a Laminar Airflow Unit or LAF).
单向气流（UDAF）单元—提供过滤单向气流的机柜（以前称为层流罩或 LAF）。

Worst case – A set of conditions encompassing processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared with ideal conditions). Such conditions have the highest potential to, but do not necessarily always result in product or process failure.
最差条件—指包含工艺限度和环境的一组条件，包括标准操作规程中的条件，这些条件造成工艺或产品故障的可能性最大（与理想条件相比）。这样的条件最有可能但不一定导致产品或过程失败。

Water system – A system for producing, storing and distributing water, usually compliant to a specific pharmacopeia grade (e.g. purified water and water for injection (WFI)).
水系统— 一种用于制备、储存和分配水的系统，通常符合特定的药典等级（例如：纯 化水和注射用水（WFI））。

Z –value – The temperature difference that leads to a 10 –fold change in the D –value of the biological indicators.
Z 值—导致生物指示剂 D 值变化 10 倍的温差。