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GUIDELINES

指南

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

欧盟药品管理规则

第 4 卷 欧盟人用和兽用药品生产质量管理规范指南

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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.

发布本指南的法律背景： 2001/83/EC 号指令第 47 条——共同体人用药品规范，以及法规 2019/6——共同体兽用药品规范。本文件为欧盟指令（EU）2017/1572 中的人用药品、指令 91/412/EEC 中的兽用药品，委员会委托条例（EU）2017/1569 中的人用研究用药品提供了药品生产质量管理规范（GMP）原则和指南的技术指导，并补充了法规（EU）536/2014 临床研究中的检查安排。

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部门实施欧盟法规，欧盟法规最终解释权归欧盟法院所有。

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

文件状态：2007 版附录 1 修订版。

Document History 文件历史

Previous version dated 30 May 2003, in operation since 2003 年 5 月 30 日版本	September 2003 2003 年 9 月起实施
Revision to align classification table of clean rooms, to include guidance on media simultations, bioburden monitoring and capping of vials 修订：调整洁净室分级表，新增培养基模拟罐装、生物负载监测和西林瓶轧盖相关指南	November 2005 to December 2007 2005 年 11 月-2007 年 12 月
Date for coming into operation and superseding 生效/取代	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.

	注：西林瓶轧盖相关规定自 2010 年 3 月 1 日起实施。

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.

变更原因：GMP/GDP 检查员工作组和 PIC/S 委员会共同建议对现行版附录 1 无菌药品生产进行修订，反映监管和生产环境的变化。新指南应阐明生产商如何通过使用 ICH Q9 和 Q10 指南中的新型工具，加深对工艺的理解，从而创造并利用新的可能性。

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.

附录 1 的修订还应考虑其它 GMP 章节和附录以及其它法规文件中的相关变更。修订后的指南将力求保证一致性，消除歧义，并将技术的进步考虑进来。

Deadline for coming into operation:

最后生效期限：

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

2023 年 8 月 25 日：自 Eudralex 第 4 卷发布发布日期后一年

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

2024 年 8 月 25 日：第 8.123 节为 Eudralex 第 4 卷发布日期后两年

Document map 目录

Section Number 章节	General overview 概述
1. Scope 范围	Includes additional areas (other than sterile products) where the general principles of the annex can be applied. 包括本附录的一般原则适用的（无菌产品以外的）其它领域。
2. Principle 原则	General principles as applied to the manufacture of sterile products. 适用于无菌产品生产的一般原则。
3. Pharmaceutical Quality System (PQS) 药品质量体系（PQS）	Highlights the specific requirements of the PQS when applied to sterile products. 强调 PQS 适用于无菌产品时的具体要求。
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. 有关具体厂房设计需求的一般性指导，以及关于厂房确认的指导（包括屏障技术的使用）。
5. Equipment 设备	General guidance on the design and operation of equipment. 关于设备的设计和运行的一般性指导。
6. Utilities 公用设施	Guidance regarding the special requirements of utilities such as water, gas and vacuum. 关于水、气、真空等公用设施的特殊要求的指导。
7. Personnel 人员	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance regarding the qualification of personnel. 关于具体培训、知识和技能要求，以及关于人员资质确认的指导。
8. Production and specific technologies 生产和具体技术	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. 关于无菌工艺和终端灭菌工艺采用的方法的指导。关于产品、设备和包装组分的灭菌方法的指导。以及针对使用特定要求的各种技术的指导，如冻干和成型-灌装-密封。
9. Environmental and process monitoring 环境监测和工艺监测	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. 本章与第 4 章的指导不同，本章适用于对系统设计、行动限警戒限设定以及趋势数据回顾的持续日常监测。 The section also gives guidance on the requirements of Aseptic Process Simulations (APS). 本章还给出了无菌工艺模拟（APS）要求的指导。
10. Quality control (QC) 质量控制（QC）	Guidance on some of the specific Quality Control requirements relating to sterile products. 与无菌产品相关的一些具体质量控制要求的指导。
11. Glossary 术语表	Explanation of specific terminology. 特定术语的解释。

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多种无菌产品类型（原料药，辅料，内包装材料和成品制剂），包装规格（单剂量到多剂量），工艺（从高度自动化系统到手动工艺）和技术（如生物技术、传统小分子生产系统和密闭系统）。本附录提供了采用质量风险管理（QRM）原则的所有无菌产品生产所用设施、设备、系统和规程的设计和控制应施用的总体指导原则，以确保最终产品中无微生物、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.

QRM 缩写适用于本文件全文，通常不会在特定段落中加以说明。如已规定具体限度、频率或范围，这些规定值应视为最低要求。此类描述是基于曾出现问题的历史监管经验制定的，这些问题已经影响了患者的安全。

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。其中部分原则和指导，例如污染控制策略、厂房设计、洁净室分级、确认、验证、监测和人员更衣等，可用于支持其它非无菌但须控制和减少微生物、微粒和内毒素/热原污染的产品的生产（例如某些液体、乳膏、软膏和低微生物负载的生物中间体）。如果生产商选择将本指南应用于非无菌产品，则应明确记录所应用的原则，并确认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特殊要求，以尽量降低微生物、微粒和内毒素/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、设备和工艺应按照药品生产质量管理规范（GMP）指南的相关章节进行适当的设计、确认和/或验证，并在适用的情况下进行持续确认。应考虑采用适当的技术（例如限制进入隔离系统（RABS）、隔离器、自动化系统、快速/替代方法和连续监测系统），加强对产品的保护，使其免受潜在的外来内毒素/热原、微粒和微生物污染源（例如人员、物料和周围环境）的影响，并帮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.

人员应具备合适的资质和经验，接受过相应培训，掌握行为规范，注重遵循生产、包装和发运过程中保护无菌产品的相关原则。

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.

无菌产品生产工艺和监测系统应由具备适当工艺、工程和微生物知识的人员设计、调试、确认、检测和定期回顾。

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.

原材料和包装材料应得到充分控制并进行检测，确保生物负载水平和内毒素/热原满足使用要求。

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.

工艺、设备、设施和生产活动应按照 QRM 原则进行管理，从而为潜在质量风险的识别、科学评估及控制提供一种前瞻性方法。如要使用替代方法，应有适当的原理依据、风险评估和缓解措施作为支持，并应符合本附录的主旨。

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.

QRM 应首先考虑设施、设备和工艺的适当设计，然后是设计良好的规程的执行，最后是证明设计和规程已正确执行并持续符合预期的监测系统的应用。仅通过监测或检测不能保证无菌性。

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.

污染控制策略（CCS）应在整个设施内实施，从而明确所有关键控制点，并评估所有用于管理药品质量和安全风险的控制措施（设计，程序性、技术性和组织性措施）和监测措施的有效性。CCS 的综合策略应建立起强有力的污染预防保障。应积极回顾并适当更新 CCS，并应推动生产和控制方法的持续改进。CCS 的有效性应成为定期管理回顾的一部分。如果控制系统已经建立并得到了妥善管理，则这些系统可能不需要更换，但应在 CCS 中提及，并应了解系统之间在相关方面的相互作用。

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.

为尽可能降低微生物、内毒素/热原和微粒的污染风险所采取的污染控制和步骤包括一系列相互关联的事件和措施。它们通常分开评估、控制和监测的，但应综合考虑它们的共同有效性。

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).

制定 CCS 需要深厚的技术和工艺知识。潜在的污染源包括微生物、细胞碎片（例如热原、内毒素）以及颗粒物（例如玻璃屑和其它可见异物和不溶性微粒）。

Elements to be considered within a CCS should include (but are not limited to):

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.

工厂和工艺的设计，包括相关的文件记录。

ii. Premises and equipment.

厂房和设备。

iii. Personnel.

人员。

iv. Utilities.

公用设施。

v. Raw material controls - including in-process controls.

原辅料控制——包括过程控制。

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.

供应商审批——例如关键部件供应商，组件和一次性系统（SUS）灭菌服务及关键服务供应商。

viii. Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services.

对外包活动的管理以及关键信息在各方之间的可用性/转移，例如：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.

灭菌工艺的验证。

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——按照确保没有额外污染风险的标准，对设备、公用设施和厂房进行维护（包括计划内和计划外维护）。

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——包括针对引入科学合理的替代方法来优化环境污染检测的可行性评估。

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、确定根本原因、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 应考虑污染控制的所有方面，并进行持续、定期的回顾，酌情更新药品质量体系。现行体系如有变更，应在实施前后评估对 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.

生产商应采取所有必要的步骤和预防措施，保证其设施内生产的产品的无菌性。不应仅依靠任何终端工艺或成品检验来确保无菌性或其它质量要素。

3 Pharmaceutical Quality System (PQS) 药品质量体系（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产品质量。因此，生产商的 PQS 应涵盖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，以尽可能降低无菌产品中的微生物、微粒和内毒素/热原污染风险。除 GMP 指南（第 1 部分——药品的基本要求）中的 PQS 具体要求外，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.

将有效的风险管理系统纳入产品生命周期的各个方面，旨在尽可能减少微生物污染并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.

生产商对所生产的产品以及对产品质量有影响的设备、工程和制造方法具备充分的知识和专业技能。

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、工艺或设备失败进行根本原因分析，正确识别和理解产品风险，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 的制定和维护中进行风险管理，来识别、评估、减少/消除（如适用）和控制污染风险。风险管理应书面化，并应包括降低风险和接受剩余风险有关决策的理由。

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地监督。风险管理的成效应作为持续质量管理的一部分进行定期审查；此外，在变更期间、出现重大问题，以及定期产品质量回顾期间也应进行审查。

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.

与无菌产品的最终处理、贮存和运输相关的过程不应损害无菌产品。应考虑的方面包括：容器完整性，污染风险，以及通过确保产品按照注册贮存条件贮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/放行的人员应能适当获取生产和质量信息，并具备无菌产品生产及其相关关键质量属性方面的足够知识和经验，从而确保这些人员能够辨别无菌产品是否按照注册的质量标准和批准的工艺生产并符合质量要求。

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.

所有不合格情况应在批次认证/放行之前充分调查，例如无菌检验不通过、环境监测异常或偏离既定程序的偏差等。调查中，应确定不合格情况对工艺和产品质量的潜在影响，以及是否有可能影响任何其它工艺或批次。某一产品或批次纳入调查范围或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，应通过更衣室（起到人员气锁及设备和物料气锁的作用）进入洁净室。洁净室和更衣室应保持适当的洁净度标准，并通过适当效率的过滤器送风。控制和监测应经过科学论证，并应有效地评估洁净室、气锁和传递窗的环境条件的状态。

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.

部件准备、产品制备和灌装的各种操作应通过洁净室或设施中适当的技术和操作隔离措施进行，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.

限制性进入隔离系统（RABS）或隔离器有利于确保所需的条件，并最大限度减少关键区直接人为干预措施引起的微生物污染。在 CCS 中应讨论它们的使用。如要采用任何方法替代 RABS 或隔离器，应证明该替代方法的合理性。

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

在无菌产品的生产中，洁净室/区分为四个等级。

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：进行高风险操作的关键区域（例如，无菌生产线，灌装区，胶塞加料盘，敞口内包装或在初始气流保护下进行无菌连接）。通常情况下，这种条件是通过局部气流保护实现的，例如 RABS 或隔离器内的单

向流操作台。应证明并确认整个 A 级区的单向流维护状态。应通过厂房、设备、工艺和程序性设计尽量减少操作人员对 A 级区的直接干预（例如，不使用隔离器和手套箱技术作为保护）。

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：对于无菌制备和灌装，这是 A 级的背景洁净室（非隔离器）。应持续监测压差。在使用隔离器技术的情况下可考虑低于 B 级的洁净室（参见第 4.20 节）。

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：在无菌灌装的无菌产品的生产中执行不太关键步骤或作为隔离器的背景的洁净室。也可用于终端灭菌产品的制备/灌装。（关于最终灭菌活动的具体细节参见第 8 章）。

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，所有暴露的表面应光滑、无渗漏性且无破损的，以尽量减少微粒或微生物的脱落或累积。

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.

为了减少灰尘累积并便于清洁，不应有难以有效清洁的凹槽，因此应最大程度减少突出的窗台、搁架、柜子和设备。门的设计也应避免不能清洁的凹槽，因此滑动门可能并不可取。

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.

无论是建材还是在房间内使用的物品，洁净室选用的材料应尽量减少微粒的产生，并且可反复使用清洁剂、消毒剂和杀泡子剂。

4.8 Ceilings should be designed and sealed to prevent contamination from the space above them.

吊顶应经过设计和密封以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 级区应禁止使用水槽和地漏。在其它洁净室中，应在机器或水槽和地漏之间安装空气隔断装置。较低等级洁净室的地漏应带存水弯或水封以防止倒灌，并定期清洁、消毒和维护地漏。

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域的转移是最大的潜在污染源之一。任何有可能损害洁净室或关键区洁净度的活动都应进行评估，如果不能取消这些活动，应采取适当的控制措施。

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、设备和组件传递至 A 级或 B 级区。应尽可能将物品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除热原烘箱/隧道）进行灭菌，然后再传递至这些区域。如果不能在物品传递时进行灭菌，应验证并采用可实现相同目的（不引入污染）的程序（例如，使用有效的转移消毒程序，隔离器的快速传递系统，或者气态或液态物料的除菌过滤器）。应通过单独的单向流程将物品（例如，物料、废物、环境样品）从 A 级和 B 级区移出。如果无法实现，应考虑按程序实现传递（物料进/出）时间上的分离，并采取控制措施，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:

气锁的设计和使用应能提供物理隔离并最大程度减少不同区域的微生物和微粒污染，物料和人员在不同级别之间的移动都应设置气锁。在可能的情况下，用于人员移动的气锁和用于物料移动的气锁应分隔开。如果无法实现，应考虑按程序实现移动（人员/物料）时间上的分离。气闸应使用经过滤的空气有效吹扫，确保洁净室的洁净级别得到保持。在“静态”状态下，气锁的最后阶段应与目标洁净室的洁净级别相同（活

性粒子和总微粒）。进入和离开 B 级区最好采用单独的更衣室。如果无法实现，应考虑按程序实现活动（进/出）时间上的分离。当 CCS 表明污染的风险很高时，进入和离开生产区应各自使用单独的更衣室。气锁的设计应遵循如下原则：

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.

人员气锁：用于人员进入的洁净级别越来越高的区域（例如从 D 级区到 C 级区到 B 级区）。一般而言，洗手设施应仅设置在更衣室的第一阶段，且不能设置在直接进入 B 级区的更衣室中。

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

物料气锁：用于物料和设备传递。

• 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.

仅允许包含在已批准清单中、在转移验证中评估的物料和设备可以通过气锁或传递窗传递到A级或B级区。设备和物料（预计用于 A 级区）在通过 B 级区传递时，应受到保护。任何需要转移的未获批物品应作为例外得到预先批准。按照生产商的 CCS，应用和记录适当的风险评估和缓解措施，包括经质量保证批准的特定的消毒和监测程序。

• 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级别的环境，例如通过供应主动过滤空气进行有效风淋。

• 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等级别或未分级区域移动到较高级别洁净区时，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.

进出传递窗和气锁（物料和人员）的门不应同时打开。对于通向 A 级和 B 级区的气锁，应采用互锁系统。对于通向 C 级和 D 级区的气锁，应至少采用视觉和/或听觉报警系统。如果需要保持区域隔离，应确定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.

在所有动态条件下，应向洁净室供应经过滤的空气以维持正压和/或与较低级别洁净环境等级相同的气流，并应有效吹扫该区域。不同级别的相邻房间的压差应至少为 10 帕斯卡（指导值）。应特别注意关键区域的保护。如果需要防止某些物料（例如致病性、高毒性或放射性产品或活病毒或活细菌物料）污染时，有关送风和压力的建议可能需要修改。修改可能包括使用正压或负压气锁防止有害物料污染周围区域。对某些操作来说，可能需要对设施（例如，洁净室和空调系统（HVAC））进行清洁，以及对离开洁净区的空气进行处理。如果防护措施要求空气流入关键区域，空气源应来自同一或更高级别的区域。

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.

洁净室和区域内的气流流型应可视化，证明空气没有从较低级别区域进入到较高级别区域，并且空气不会来自不太洁净的区域（例如地板）或经过可能将污染转移到较高级别区域的操作员或设备。在需要使用单向流的地方，应进行可视化研究以确定是否符合要求（参见 4.4 和 4.19 节）。当已灌封的产品通过一个小的出口转移到较低级别的相邻洁净室时，气流可视化研究应证明空气不会从较低级别的洁净室进入 B 级区。当空气流动显示出对洁净区或关键区域的污染风险时，应采取纠正措施，例如设计改进。应在静态和动态

（例如模拟操作员干预）条件下进行气流流型研究。应保留气流流型的录像。应记录空气可视化研究的结果，并在确定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器。CCS 中应考虑设置点和压差的关键性。确定为关键的压差应受到持续监测和记录。应设置报警系统，在送风失败或压差降低（被确定为关键的压差低于设定限度）时立即指示和警告操作人员。报警信号不应在未经评估的情况下被覆盖，应有程序概述发出报警信号时应采取的措施。如果设置了报警延迟，应在 CCS 内进行评估和论证。其它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 级区外观察生产活动（例如，通过窗户或远程摄像头全方位查看这些区域和工艺过程，以便在不进入的情况下进行观察和监督）。在设计新设施或翻新现有设施时，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（两种不同的技术）及其相关工艺的设计中，应通过将 A 级环境与周围房间环境分隔来提供保护。应尽量减少工艺过程中物品进出所带来的危害，并通过高性能转移技术或经过验证的系统提供支持，其能有效防止污染且适合于各自的技术。

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.

所用技术和工艺的设计应确保在关键区域维持适当的条件，从而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通过关键区域的初始气流保护和工艺过程中暴露产品上方和周围的单向流吹扫保证 A 级条件。

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通过工艺过程中充分保护暴露产品保证 A 级条件。在进行简单操作的封闭式隔离器中，气流可能不是完全单向的。然而，任何湍流不应增加暴露产品的污染风险。当生产线包含在封闭式隔离器中时，应通过关键区域的初始气流保护和工艺过程中暴露产品上方和周围的单向流吹扫保证 A 级条件。

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.

只当有必要进行产品防护（例如放射性药品）才可使用负压隔离器，并且应采用专门的风险控制措施以避免关键区域受到影响。

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 的设计应通过具有单向流和关键区域初始气流保护确保 A 级条件。应保持从关键区到支持性背景环境的正向气流。

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.

开放式隔离器的环境通常应至少为 C 级。封闭式隔离器的背景应至少为 D 级。背景级别的决定应基于风险评估并在 CCS 中论证合理性。

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.

当进行隔离器 CCS 的风险评估时，关键考虑因素应包括（但不限于）：消毒程序，自动化程度，可能影响关键工艺点“初始气流”保护的手套操作的影响，屏障/手套完整性的潜在损失的影响，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的活动（例如安装或维护）。当发现其它工艺风险时，应考虑更高级别的背景，除非在 CCS 中进行了适当的论证。

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.

用于无菌工艺的RABS的环境应至少为B级，并且应进行气流流型研究以证明在干预过程中没有空气进入，包括开门（如适用）。

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.

应证明手套系统（用于隔离器和 RABS）的材料具有适当的机械和化学抗性。应在 CCS 中规定更换手套的频率。

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.

对于隔离器，应使用证明适合于任务和关键性的方法对手套系统进行检漏。应定期进行测试。一般来说，手套完整性测试至少应在每个批次或阶段性生产的开始和结束时进行。根据经过验证的阶段性生产长短，可能需要进行额外的手套完整性测试。

Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.

手套完整性监测应包括与每次使用相关的目视检查，以及可能影响系统完整性的任何操作后的目视检查。

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.

对于生产单剂量或小批量的手动无菌工艺活动，完整性确认的频率可基于其它标准（例如每个生产周期的开始和结束）。

b. Integrity / leak testing of isolator systems should be performed at defined intervals.

应定期进行隔离器系统的完整性/检漏测试。

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，A 级区使用的手套应在安装前进行灭菌，并在每次生产活动之前通过经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。在每次使用时目视检查手套，并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.

应适当规定和控制去污染的方法（清洁和消毒，以及适用时生物材料的灭活）。消毒步骤之前的清洁非常重要：任何残留物可能会抑制去污染过程的有效性。还应提供证据证明使用的清洁和消毒剂不会对 RABS 或隔离器内生产的产品产生不良影响。

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.

内部的消毒过程应是自动化的、经过验证的，应控制在规定的周期参数范围内，并应包括适当形式的杀孢子剂（例如气态或汽化形式）。手套应展开，五指分开，与杀孢子剂充分接触。所用方法（清洁和杀孢子生物消毒）应确保隔离器的内部表面和关键区域不存在活的微生物。

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.

杀孢子消毒应包括常规应用杀孢子剂，使用的方法应经验证并证明能有效地涵盖部表面所有区域并确保环境适合无菌工艺。

Cleanroom and clean air equipment qualification

洁净室和洁净空气设备的确认

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，如单向流单元（UDAF）、RABS 和隔离器，应根据所要求的环境特性进行确认。每个生产操作都要求在动态条件下达到适当的环境洁净度水平，最大程度降低所处理的产品或物料的污染风险。应维持“静态”和“动态”下的适当洁净度水平。

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.

应使用符合附录 15 要求的方法对洁净室和洁净空气设备进行确认。洁净室确认（包括分级）应与动态环境监测明确区别开来。

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分级的洁净室或洁净空气设备与其预期用途的符合程度的整体过程。作为附录 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（与设施的设计/运行相关的）：

i. Installed filter system leakage and integrity testing.

已安装的过滤器系统的检漏和完整性测试。

ii. Airflow tests - volume and velocity.

气流测试——体积和流速。

iii. Air pressure difference test.

压差测试。

iv. Airflow direction test and visualisation.

气流方向测试和可视化。

v. Microbial airborne and surface contamination.

浮游菌和表面污染

vi. Temperature measurement test.

温度测定测试。

vii. Relative humidity test.

相对湿度测试。

viii. Recovery test.

自净测试。

ix. Containment leak test.

容器检漏测试。

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可参考 ISO 14644 系列标准。

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，是一种根据洁净室或洁净空气设备的标准通过测定总微粒浓度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产生任何影响。例如，应在模拟操作期间进行初步分级，在模拟操作或无菌工艺模拟试验（APS）期间进行再分级。

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.

对于洁净室分级，应测定等于或大于 0.5μm 和 5μm 的微粒总数。应按照表 1 中规定的限度，在静态和模拟操作中进行测定。

Table 1: Maximum permitted total particle concentration for classification

表 1：各级别允许的最大总微粒浓度

Grade 级别	Maximum limits for total particle 总粒子数最高限度 $> 0.5 \mu m/m^3$		Maximum limits for total particle 总粒子数最高限度 $> 5 \mu m/m^3$	
	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) 未预先确定	29 300	Not predetermined (b) 未预先确定

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

在 CCS 或历史趋势中有说明的情况下，可以考虑包括 5μm 微粒的分级。

(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 级区，没有预先确定的动态限度。生产商应根据风险评估和适用的常规数据建立动态限度。

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，采样点的最小数量及其位置可参见 ISO 14644 第 1 部分。对于无菌工艺区及其环境（分别为 A 级和 B 级区），应考虑额外的采样位置，并应评估所有关键操作区，例如灌装点和包材进料斗。关键操作位点应通过有书面的风险评估以及对该区域所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.

洁净室分级应在“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”是指所有公用设施（包括任何正常运行的 HVAC）已安装完成、主生产设备按规定安装但未运行、并且无人员在场的状态。

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”是指洁净室安装完成、HVAC 系统全面运行、设备已安装并按照生产商规定的运行模式运行、并且有最大数量的操作人员在场执行或模拟日常操作的状态。

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.

应在操作和生产线清场/清洁活动完成后的“自净期”达到表 1 给出的“静态”总微粒限度。“自净期”（指导值小于 20 分钟）应在房间确认过程中确定，在程序中进行记录并遵守，以便在操作过程中洁净度受到损坏的情况下，将房间恢复到经确认的洁净状态。

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.

单向流系统送风速度的合理性应在确认方案中明确论证，包括风速的测定位置。风速的设计、测定和维持应确保在工作区域（例如，在进行高风险操作的区域以及产品和/或组分暴露的区域）有合适的单向气流为产品和开放组件提供保护。除非在 CCS 中另有科学论证，否则单向流系统应在工作区域提供 0.36-0.54m/s（指导值）的均匀风速。气流可视化研究应与风速测定相关联。

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.

洁净室的微生物污染水平应作为洁净室确认的一部分进行确定。采样点的数量应基于书面的风险评估、房间分级结果、气流可视化研究以及对该区域要进行的工艺和操作的了解。表 2 给出了各级别确认过程中的微生物污染最大限度。确认包含“静态”和“动态”条件中。

Table 2: Maximum permitted microbial contamination level during qualification

表 2：确认过程中允许的最大微生物污染水平

Grade 级别	Air sample 浮游菌 CFU/m^3	Settle plates (diameter 90 mm) CFU/4 hours(3) 沉降菌（直径 90mm） CFU/4 小时	Contact plates (diameter 55 mm) CFU/plate 表面微生物（直径 55mm） CFU/碟
A	No growth 无生长		
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.

沉降碟应在操作期间暴露，并在最多 4 小时后按需要更换。暴露时间应基于回收率研究，并且避免所所用培养基干燥。

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：指示表中具体级别的所有方法应用于该级别区域的确认。如果不采用表格中的某种方法，或使用替代方法，应进行适当论证。

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：在整个文件中使用 CFU 表示限度。如果采用不同的或新的技术并且结果不以 CFU 的方式呈现，生产商应科学地论证其限度，并尽可能将其与 CFU 相关联。

Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply.

注 3：对于人员更衣的确认，应采用表 6 中的表面微生物和五指手套的限度要求。

Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.

注 4：采样方法不应给生产操作带来污染风险。

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:

洁净室和洁净空气设备的再确认应按照规定的程序定期执行。再确认应至少包括以下内容：

- Cleanroom classification (total particle concentration).

洁净室分级（总微粒浓度）。

- Integrity test of final filters.

最终过滤器的完整性测试。

- Airflow volume measurement.

气流量测定。

- Verification of air pressure difference between rooms.

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，风速测试应按照风险评估的结果进行，并将该风险评估包含到 CCS 中。但是，使用单向流的灌装区（例如，灌装最终灭菌产品时或 A 级和 RABS 的背景区）需要进行测试。对于非单向流的级别，应以自净测试代替风速测试）。

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:

在纠正设备或设施缺陷而采取的整改措施完成后，或设备、设施或工艺的变更后，还应视情况进行上述检测进行适当的再确认。变更的重要性应通过变更管理规程确定。需要考虑的变更案例包括但不限于：

i. Interruption of air movement which affects the operation of the installation.

气流中断，影响装置的运行。

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 系统的操作设定参数的变更。

iii. Special maintenance which affects the operation of the installation (e.g. change of final filters).

影响装置操作的特殊维护（例如最终过滤器的更换）。

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).

洁净室的消毒尤为重要。应根据书面程序彻底清洁洁净室并消毒。消毒前应清洁以去除表面污染物，确保消毒有效。清洁程序应有效去除消毒剂残留。应使用一种以上的消毒剂，确保这些消毒剂有不同作用机制，其联合使用能有效杀灭细菌和真菌。消毒应包括定期使用杀孢子剂。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（例如，对目前使用的消毒方式产生抗性的微生物）。

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.

消毒工艺应经过验证。验证研究应证明以特定方式使用消毒剂以及消毒剂对表面材料或代表性材料（如经论证）的适用性和有效性，并应支持制备溶液的使用有效期。

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.

A 级和 B 级区使用的消毒剂和清洁剂在使用前应为无菌状态。如在 CCS 中确定，C 级区和 D 级区使用的消毒剂也可能要求无菌。当消毒剂和清洁剂由无菌产品生产商稀释/制备时，应以防止污染的方式进行，并应监测微生物污染。稀释液应保存在预先清洁过（且灭菌过，如适用）的容器中，并且只能保存规定时长。如果消毒剂和清洁剂为预制品，在对供应商资质进行适当的确认后，可以接受分析报告单或合格证上的结果。

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.

如果洁净室和相关表面使用熏蒸或蒸汽消毒（例如过氧化氢蒸汽），应了解并验证所有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.

应提供关于设备设计的书面详细说明（包括流程图和管道设备图，如适用）。该说明应为初始确认文件包的一部分并持续更新。

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”中进行定义，并在确认过程中予以确认。应确认工艺和设备报警事件，并评估其趋势。评估报警的频率应基于报警的关键程度（关键报警立即审核）。

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.

设备及辅助装置和服务的设计和安装方式，应尽可能地使操作、维护和维修在洁净室外进行。如果必须在洁净室中进行维护，并且无法维持所要求的洁净和/或无菌标准，则应当考虑预防措施，例如限制指定人员进入工作区，建立明确的工作方案和维护程序。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，应尽可能在重新组装完成后灭菌。

5.4 The cleaning process should be validated to be able to:

清洁程序应进行验证，确保其能够：

i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.

去除对使用的消毒剂的有效性产生不利影响的所有残留物或碎片。

ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

在工艺过程中和消毒前尽可能减少产品的化学、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，直接和间接接触产品的部件应进行灭菌。直接接触产品的部件是指产品通过的部件，例如灌装针或泵。间接接触产品的部件是不接触产品的设备部件，但可能与其它灭菌表面接触，其无菌性对整个产品的无菌性至关重要（例如胶塞桶和导槽等已灭菌物品，以及已灭菌组件）。

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，均应进行确认、监测和计划性维护。维护完成后，方可批准恢复使用。

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.

当要进行对产品无菌性至关重要的设备计划外维护时，应评估并记录对产品无菌性的潜在影响。

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).

除传送带本身能连续灭菌（如隧道式灭菌器）以外，传送带不得穿越 A 级或 B 级区与低级别工艺区的隔离墙。

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.

粒子计数器，包括采样管，应经确认。对于管径和弯曲半径，应考虑生产商建议的标准。除非另有正当理由，否则管长通常应不超过 1 米，并且应尽量减少弯曲。在测定房间级别时，应使用采样管较短的便携式粒子计数器。在单向流系统中应使用等速采样头。采样头应朝向适当并尽可能靠近关键位置，以确保样品具有代表性。

6 Utilities 公用设施

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.

公用设施系统所用控制措施的性质和程度应与该公用设施相关的产品质量风险相称。应通过风险评估来确定其影响并进行记录，作为 CCS 的一部分。

6.2 In general, higher risk utilities are those that:

一般来说，风险较高的公用设施指的是：

i. Directly contact product e.g. water for washing and rinsing, gases and steam for sterilisation.

直接接触产品，例如：用于清洗和淋洗的水，用于灭菌的气体和蒸汽。

ii. Contact materials that will ultimately become part of the product.

最终成为产品一部分的接触物料。

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.

以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.

公用设施的设计、安装、确认、操作、维护和监测方式应确保该公用设施系统按预期运行。

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.

高风险公用设施的关键参数和关键质量属性的结果应定期进行趋势分析，以确保系统性能保持适当。

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:

公用设施系统的整个生命周期内应始终保存其安装记录。此类记录应包括现行图纸和示意图，建筑材料清单和系统标准。通常，重要信息包括以下方面：

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

管道流向、斜率、直径和长度。

ii. Tank and vessel details.

罐和容器的详细信息

iii. Valves, filters, drains, sampling and user points.

阀、过滤器、排水设施、取样点和使用点。

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.

洁净室内不应存在管道、风管等设施。如果此类设施不可避免，则安装时应确保不会产生凹槽、未密封的开口和难以清洁的表面。安装应便于管道外表面的清洁和消毒。

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.

水处理设施及其分配系统地设计、建造、安装、调试、确认、监测和维护应防止微生物污染，并确保高质量的可靠水源。应采取措施，最大程度降低微粒、微生物污染/增殖和内毒素/热原的风险（例如倾斜管道以完全排水以及避免死角）。当系统中包含过滤器时，应特别注意对其进行监测和维护。产出的水应符合相关药典的现行各论。

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.

水系统应经过确认和验证，能维持适当的物理、化学和微生物控制水平，并考虑到季节变化的影响。

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.

水流在水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及随后生物膜形成的风险。应在确认过程中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）应使用符合质量标准（在确认过程中定义）的水来制备。WFI 的存储和分配方式应最大程度地降低微生物生长风险（例如在 70℃以上温度持续循环）。WFI 应通过蒸馏或等同于蒸馏的纯化工艺生产。这可能包括反渗透与其他适当技术的结合，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 储罐配有疏水性除菌过滤器，过滤器不应成为污染的来源，并应在安装前和使用后进行过滤器的完整性测试。应采取控制措施，防止在过滤器上形成冷凝水（例如加热）。

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.

为最大程度降低生物膜形成的风险，应按照预定的时间表对水系统进行灭菌、消毒或再生，并作为超限或超标后的整改措施。用化学品对水系统进行消毒后，用经过验证的程序进行淋洗/冲洗。应在消毒/再生后进行水质检测。在水系统恢复使用之前，化学检验结果应得到批准，并且在使用该系统的水生产的批次得到认证/放行之前，微生物/内毒素结果应经过核实在质量标准范围内并得到批准。

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.

应对水系统定期进行化学和微生物监测，确保水始终满足药典要求。警戒限应基于初次确认数据设置，并根据后续再确认、日常监测和调查中获得的数据进行定期再评估。应对持续监测数据进行回顾，及时发现系统性能的任何不良趋势。取样计划应反映 CCS 的要求，涵盖所有出口和用水点，并规定时间间隔，以确保定期获取有代表性的水样用于分析。取样计划应基于确认数据制定，考虑潜在最差条件取样点，并应确保每天至少包括一个具有代表性的生产工艺用水样品。

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.

偏离警戒限的异常情况应进行记录和审核，包括调查确定偏离是否为单个（独立）事件，或结果是否表明不良趋势或系统恶化。应对偏离行动限的每个异常情况进行调查，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.

WFI 系统应包括连续监测系统，监测总有机碳（TOC）和电导率等指标，因为这些参数比离散取样更好地指示整体系统性能。传感器位置应基于风险。

Steam used as a direct sterilising agent

直接灭菌用蒸汽

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）发生器的原水应适当净化。纯蒸汽发生器的设计、确认和操作方式应确保产生的蒸汽的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.

直接灭菌用蒸汽应具有适当的质量，并且所含添加剂的量不应给产品或设备造成污染。对于提供用于直接灭菌物料或产品接触表面的纯蒸汽的发生器（例如多孔硬物高压蒸汽灭菌柜），蒸汽冷凝水应符合相关药典的现行 WFI 各论（蒸汽冷凝水的微生物检测不是强制性的）。应制定合适的取样计划，以确保定期获得代表性的纯蒸汽用于分析。灭菌用纯蒸汽的其它质量方面应按照经验证的参数定期评估。这些参数应包括以下（除非另有说明）：非冷凝性气体，蒸汽干度值（干度分数）和蒸汽过热值。

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、微粒和微生物质量。所有相关参数，包括含油率和含水量，应进行规定，设置参数时应考虑到气体的使用和类型、气体发生系统的设计，且符合相关药典的现行各论或产品质量要求（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.

在无菌工艺中使用的气体应在使用点通过除菌级过滤器（标称孔径最大为 0.22μm）过滤。如果过滤器是按产品批次使用（例如用于过滤无菌灌装产品的表层气体）或作为产品容器的呼吸过滤器，则过滤器应进行完整性测试，并将结果作为批次认证/放行的一部分进行审核。所有位于最终除菌级过滤器之后的输送管道均应进行灭菌。当工艺中使用气体时，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.

如果真空或压力系统的回流会对产品造成潜在风险，应采取措施阻止真空系统或压力系统关闭时产生的回流。

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.

液压、加热和冷却系统相关的设备主要部分应尽可能位于灌装室外。应有适当的控制措施来处理与系统液体相关的任何泄漏和/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).

对产品造成风险的系统泄漏应是可检出的（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.

生产商应确保具有足够数量的合适人员，这些人员在无菌产品生产和检验以及该场地生产操作所用的任何具体生产技术方面经过适当的资质确认、培训并富有经验，以确保符合无菌产品生产和处理相关 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.

洁净室只应有所需最低数量人员在场。应在某些活动（如初始确认和 APS）期间确定、记录并考虑洁净室操作人员的最大数量，以确保不会损害无菌保证。

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.

所有人员，包括执行清洁、维护、监控以及进入洁净室的人员，均应定期接受无菌产品正确生产相关纪律的培训、更衣确认和评估。该培训应包括微生物学和卫生学的基本要素，特别关注洁净室实践、污染控制、无菌技术和无菌产品的保护（对于进入 B 级洁净室和/或干预 A 级的操作人员）以及产品非无菌对患者的潜在安全性影响。培训水平应基于人员职能以及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 级区的人员应接受无菌更衣和无菌行为的培训。应通过评估和至少每年定期再评估来确认符合无菌更衣规程，并应包括目检和微生物评估（使用戴手套的手指、前臂、胸部和头罩（口罩/额头）等监测位置。预期限度参见 9.30 节）。对于正在或即将进行无菌操作的 A 级和 B 级区，无监督进入应仅限于经过适当资质确认、已通过更衣评估并参与过成功的 APS 的人员。

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应进入 B 级洁净室或 A 级（动态）。如果在例外情况下需要进入，生产商应制定书面程序，概述未经资质确认的人员被带入 B 级区和 A 级区的流程。生产商经批准的人员应在未经资质确认人员的活动期间对其进行监督，并应评估这些活动对该区域洁净度的影响。这些人员的进入应按照 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.

应有关于取消人员在洁净室工作或取消人员无监督进入洁净室资格的系统，基于的依据包括持续评估和/或识别该人员监测计划的不良趋势和/或参与的 APS 失败。一旦取消资格，应完成再培训和再次资质确认后才能允许该操作人员进一步参与无菌操作。对于进入 B 级洁净室或执行 A 级干预的操作人员，再次资质确认应包括是否参与成功的 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.

高标准的个人卫生和清洁对于防止过度散发脱落物或增加微生物污染风险至关重要。应当指示参与无菌产品生产的人员报告可能导致散发异常数量或类型污染物的任何特定健康状况或疾病，从而防止他们进入洁净室。对那些可能导致微生物污染风险增大的员工，应由指定的合格人员提供其健康状况和采取的措施，并在程序中加以说明。

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.

参与人体或动物组织加工处理的人员、或与当前生产无关的微生物培养的人员、或参与可能对质量有不良影响的任何活动（例如微生物污染）的人员，不应进入洁净区，除非遵循了有明确定义的，且有效的净化程序以及进入洁净区的程序，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.

不应允许将手表、化妆品、珠宝首饰、其它个人物品（如移动电话）和任何其它非必需物品带入洁净区。洁净室中使用的电子设备如果经过适当设计，符合与其使用处洁净级别的清洁和消毒要求，则可以接受，例如由生产商提供的仅用于洁净室的电话和平板电脑。CCS 中应涵盖这些设备的使用和消毒。

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.

洁净室更衣和洗手应遵循相应书面程序，该程序应旨在最大限度减少洁净服污染和/或减少污染物转移至洁净区。

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 bechecked 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.

工作服及其质量应符合工艺和工作区的级别。穿着工作服的方式应能确保产品不受污染。当选择的工作服类型需要为操作人员提供保护时，不应损害对产品的污染保护。在更衣前后，均应即时目视检查工作服的清洁度和完整性。离开洁净室后也应立刻检查工作服的完整性。对于已灭菌的工作服和护目镜，应特别注意确保它们已经过灭菌处理、在规定的保持时间内、并且已目视检查包装确保在使用前是完整的。可重复使用的工作服（包括护目镜）应在发现破损时更换，或以确认研究中确定的频率更换。工作服的确认应考虑到所有必要的工作服测试要求，包括仅通过目视检查可能无法发现的工作服破损情况。

7.12 Clothing should be chosen to limit shedding due to operators' movement.

选择的工作服应能限制由于操作人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:

各洁净级别通常要求的着装说明如下：

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 级的情况）：在更衣前应穿着无菌服下的专用工作服（参见 7.14 节）。穿上已灭菌的洁净工作服时，还应戴上经适当灭菌且无粉橡胶或塑料手套。无菌头罩应包裹所有头发（以及面部毛发），与工作服其它部分分开，并应塞入工作服的衣领中。应佩戴无菌面罩和无菌眼罩（例如护目镜），覆盖和包裹所有面部皮肤，防止面部液滴和微粒发散。应穿戴经适当灭菌的鞋类（例如高筒套靴），裤腿管应塞入套靴内。在穿工作服时佩戴的无菌手套之外再佩戴另一副无菌手套，并将袖口塞入外层手套内。防护服应最大限度减少纤维或微粒的脱落，并能保留身体散发的微粒。应在工作服确认中评估洁净服的微粒脱落和微粒保留效率。选择适当的洁净服的包装和折叠方式，使操作人员能在不接触服装外表面的情况下穿上工作服，并防止工作服接触地板。

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：应遮盖头发、胡须。应穿手腕处可收紧的高领连体服或分体式工作服，并穿适当消毒的鞋或鞋套。这类服装应尽可能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：应遮盖头发、胡须。应穿普通的防护服和适当消毒的鞋子或鞋套。应采取适当措施，以避免洁净区外的污染引入本区。

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.

在执行 CCS 确定的存在污染风险的活动时，C 级区和 D 级区可能需要额外的工作服，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洁净级别的更衣室进行，以确保维持工作服的洁净度。不得将包括袜子在内的便服（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服或分体式工作服，以及覆盖脚部的工作袜。工作服和工作袜不应对更衣区或者工艺带来污染风险。

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.

每位操作人员在每次进入 B 级或 A 级区时，都应更换合适尺寸的经灭菌的洁净防护服（包括眼罩和面罩）。应定义轮班期间更换前经灭菌的工作服的最长穿戴时间，作为工作服确认的一部分。

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.

操作过程中应定期消毒手套。如果工作服和手套损坏并存在任何产品污染风险，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.

可重复使用的洁净区工作服应在与生产操作充分隔离的洗衣设施中用经过确认的程序进行清洁，确保工作服不会在重复洗衣过程中损坏和/或被纤维或微粒污染。洗衣设施不应引入污染或交叉污染风险。处理和使用工作服不当可能会损坏纤维，并可能增加微粒脱落的风险。清洗后和包装前，应目检工作服的损坏情况和清洁度。应评估并确定工作服的管理流程，作为工作服确认计划的一部分，其中应包含最大洗衣和灭菌循环次数。

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.

洁净区中对生产过程不重要的活动应保持在最低限度，特别是在进行无菌操作时。人员移动应缓慢、受控并有条不紊，以避免由于过度活动导致的微粒和微生物的过量脱落。执行无菌操作的操作人员应始终遵循无菌技术，以防止气流的变化可能将较低质量的空气引入关键区域。应限制关键区附近的移动，应避免单向流（初始气流）通路的阻塞。应考虑将气流可视化研究的回顾作为培训计划的一部分。

8 Production and Specific Technologies 生产和具体生产技术

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.

组件和物料的制备应至少在 D 级洁净室中进行，以降低微生物、内毒素/热原和微粒污染的风险，使产品适于灭菌。当产品的微生物污染风险比较高或异常时（例如，产品很容易长菌，产品在灌装前需等待很长时间，或者产品主要不在密闭容器中加工），则应至少在 C 级环境中进行制备。软膏剂、霜剂、混悬剂和乳剂应至少在 C 级环境下进行制备，然后最终灭菌。关于兽用药品最终灭菌的详细指导见 GMP 指南附录 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使用经验证的工艺进行清洁，以确保微粒、内毒素/热原和微生物污染得到适当控制。

8.3 Filling of products for terminal sterilisation should be carried out in at least a grade C environment.

最终灭菌产品的灌装应至少在 C 级环境中进行。

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 确定环境对产品污染的风险比较大时，例如灌装操作慢，容器口径宽或密封前须暴露数秒，则产品应在至少 C 级背景的 A 级下灌封。

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.

待包装溶液的加工应包括在可能的情况下使用微生物截留过滤器的过滤步骤，以在灌装入最终产品容器之前降低生物负载水平和微粒，并且配制和灌装之间应规定最长允许时间。

8.6 Examples of operations to be carried out in the various grades are given in Table 3.

表 3 给出了各级区内操作的示例。

Table 3: **Examples of operations and grades for terminally sterilised preparation and processing operations**

表 **3**：最终灭菌产品的制备和加工的操作及洁净级别示例

Grade A	-	Filling of products, when unusually at risk.

A 级	高污染风险产品的灌装。
Grade C **C** 级	- Preparation of solutions, when unusually at risk. 高污染风险溶液的制备。 - Filling of products. 产品的灌装。
Grade D **D** 级	- Preparation of solutions and components for subsequent filling. 灌装前溶液或组件的制备。

Aseptic preparation and processing 无菌制备和加工

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.

无菌工艺应被明确定义。无菌工艺相关风险以及任何相关要求应被识别、评估并适当控制。工厂的 CCS 应明确规定这些控制的可接受标准、监测要求及其有效性审核。应描述并执行控制这些风险的方法和程序。可接受的残留风险应形成正式记录。

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.

在无菌环境下准备的过程中、在所有工艺阶段（包括待包装产品灭菌之前和之后的阶段）、以及直至产品封装入最终容器中，都应按照工厂的 CCS 采取预防措施以最大程度减少微生物、内毒素/热原和微粒污染。在洁净室应尽可能减少容易产生微粒和纤维的物料。

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).

在可能的情况下，应考虑采用 RABS、隔离器等系统，减少对 A 级区的关键干预，并将污染风险降至最低。也可考虑机器人和工艺自动化，消除直接的人为关键干预（例如干热隧道、自动装载冻干机、在线灭菌）。

8.10 Examples of operations to be carried out in the various environmental grades are given in Table 4.

各级环境下执行的操作的示例见表 4。

Table 4: **Examples of operations and grades for aseptic preparation and processing operations**

表 4：无菌准备和加工的操作及洁净级别示例

Grade A **A 级**	- Aseptic assembly of filling equipment. 灌装设备的无菌装配。 - Connections made under aseptic conditions (where sterilised product contact

	surfaces are exposed) that are post the final sterilising grade filter. These connections should be sterilised by steam-in-place whenever possible. 最终除菌过滤器后在无菌条件下（已灭菌产品的接触表面暴露处）进行的连接。这些连接应在可能的情况下经过在线蒸汽灭菌。 - Aseptic compounding and mixing. 无菌配制和混合。 - Replenishment of sterile bulk product, containers and closures. 无菌待包装产品、容器和密封件的补充。 - Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. 灭菌器中无保护（如无包装）物品的取出和冷却。 - Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. 未包裹的无菌内包装组件在无菌灌装线中的分段运输和传送。 - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. 无菌灌装，容器密封（如安瓶、西林瓶密封），敞口或半压塞西林瓶的转移。 - Loading of a lyophilizer. 冻干机的装载。
Grade B **B 级**	- Background support for grade A (when not in an isolator). A 级的背景辅助（不在隔离器中）。 - Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A. 设备、组件和辅助用品在免受周围环境影响的情况下传送或分段运输进入 A 级。
Grade C **C 级**	- Preparation of solutions to be filtered including sampling and dispensing. 待过滤约液的制备，包括取样和称量。
Grade D **D 级**	- Cleaning of equipment. 设备清洁。 - Handling of components, equipment and accessories after cleaning. 清洁后组件、设备和配件的处理。 - Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation. 灭菌前已清洁的组件、设备和配件在 HEPA 过滤气流下的装配。 - Assembly of closed and sterilised SUS using intrinsic sterile connection devices. 使用内部无菌连接装置组装已密封和已灭菌的 SUS。

8.11 For sterile products where the final formulation cannot be filtered, the following should be considered:

对于最终制剂无法过滤的无菌产品，应考虑：

i. All product and component contact equipment should be sterilised prior to use.

所有与产品和组件接触的设备应在使用前进行灭菌。

ii. All raw materials or intermediates should be sterilised and aseptically added.

所有原材料或中间体应灭菌并无菌添加。

iii. Bulk solutions or intermediates should be sterilised.

待包装药液或中间体应灭菌。

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.

与产品直接或间接接触的已灭菌设备、组件和辅助用品的拆包、装配和准备应作为无菌工艺过程，在 B 级环境下的 A 级区域内执行。无菌产品的灌装线组装和灌装应作为无菌工艺过程，在 B 级环境下的 A 级区域内执行。当使用隔离器时，背景应符合 4.20 节的规定。

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.

如果产品及其组件暴露于环境下，且产品不会进行后续过滤（通过除菌级过滤器）或最终灭菌时，无菌产品（如软膏剂、霜剂、混悬剂和乳剂）的制备和灌装应在 B 级环境下的 A 级内进行。如果采用隔离器或 RABS，其环境应符合 4.20 节的规定。

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.

无菌连接应在 B 级环境下的 A 级区域内进行，除非随后经在线灭菌或使用内部无菌连接装置，从而最大程度地降低来自周围环境的潜在污染。内部无菌连接装置的设计应降低污染风险。

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.

若采用隔离器，其环境应符合 4.20 节的规定。无菌连接应进行适当评估并确认其有效性。有关内部无菌连接装置的要求，请参见第 8.129 和 8.130 节。

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.

应通过使用预装配并灭菌的设备等工程设计方案，尽量减少无菌操作（包括非固有无菌连接装置）。与产品接触的管道和设备应尽可能预装配并在线灭菌。

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.

应制定一份清单并经过批准，列出生产过程中可能发生并经过批准和确认的干预措施（固有性措施和纠正性措施）（参见 9.34 节）。应谨慎设计干预措施，确保有效降低环境、工艺和产品的污染风险。设计干预措施时应考虑对气流、关键表面和产品的任何影响。应尽可能使用工程方案，尽量减少操作人员在干预过程中的介入。应始终遵守无菌技术，包括操作中对无菌工具的使用情况。对于列出固有性和纠正性干预措施类型以及如何执行这些干预的程序，应首先通过风险管理和 APS 进行评估，并保持更新。未经确认的干预措施应仅在特殊情况下使用，并适当考虑与干预措施相关的风险并经质量部门批准。所实施的干预措施的细节应经过风险评估、进行记录并根据生产商的 PQS 进行全面调查。质量部门应彻底评估所有未经确认的干预措施，并在批次处理过程中予以考虑。

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).

干预和停工应记录在批记录中。每次生产线的停工或干预都应在批记录中充分记录，包括相关的时间、持续时间和操作人员（参见 9.34 节）。

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:

无菌准备和加工每个方面的持续时间应尽量减少，并且应限定到已确定并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、组件和容器清洁、干燥和灭菌之间的保持时间。

The holding time for sterilised equipment, components, and containers before use and during filling/assembly.

已灭菌设备、组分和容器在使用前和灌装/装配过程中的保持时间。

iii. The holding time for a decontaminated environment, such as the RABS or isolator before use.

已净化环境（例如 RABS 或隔离器）在使用前的保持时间。

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.

产品制备、产品灭菌或通过除菌过滤器过滤（如适用）、完成无菌灌装过程三者的时间间隔。基于产品的组分和规定的贮存方法，每种产品都应设置最大允许在线保持时间。

v. The holding time for sterilised product prior to filling.

已灭菌产品在灌装前的保持时间。

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）应由具备无菌工艺专业知识的人员定期观察，核实操作（包括操作人员在洁净室内的行为）的正确性，并在发现不当操作时予以纠正。

Finishing of sterile products

无菌产品的最终处理

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).

敞口的内包装容器应置于 A 级环境中，并具有适用于技术的适当背景，如 4.20 节所述。对于半压塞的西林瓶或预填充注射器，请参见 8.126 节。

8.21 Final containers should be closed by appropriately validated methods.

最终容器应通过经活当验证的方法密封。

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.

当最终容器通过融合密封时，例如吹灌封（BFS）、成型-灌装-密封（FFS）、小容量注射剂和大容量注射剂（SVP&LVP）的袋子、玻璃或塑料安瓶瓶，应评估、确定影响密封完整性的关键参数和变量，并在操作过程中进行有效控制和监测。熔融密封的玻璃安瓿瓶、BFS 单元和小容量容器（<100 ml）应使用经验证的方法进行 100%完整性测试。对于熔融密封的大容量容器（>100 ml），在经过科学论证并基于证明现有

工艺可靠性和高水平工艺控制的数据的情况下，减少取样可能是可以接受的。值得注意的是，目检不被认为是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.

使用非融合系统的产品应进行取样并使用经验证的方法检查其完整性。完整性检查的频率应基于所使用容器和密封系统的知识和经验。应使用经科学论证的取样计划。样本量应基于供应商管理、包装组件质量标准和工艺知识等信息。

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.

在真空下密封的容器应在认证/放行前适当的预定时间后以及货架期内进行真空维持测试。

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).

容器密封完整性验证应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（例如减压或极端温度）。

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.

如果轧盖设备会产生大量非活性粒子，则应采取措施防止微粒污染，例如将设备放置在单独的工作间内，并配备适当的抽气装置。

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.

无菌灌装产品的西林瓶轧盖可使用经灭菌的瓶盖而作为无菌工艺，或作为无菌工艺区外的洁净工艺。采用后一种方法的情况下，西林瓶应受到 A 级条件的保护直至离开无菌工艺区，之后加塞的西林瓶应用 A 级送风保护直至瓶盖压合。A 级送风的辅助环境应至少满足 D 级要求。如果轧盖为手动操作，则应在 A 级条件下进行，可在经适当设计的隔离器中或在 B 级环境下的 A 级区域内。

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.

当无菌灌装的无菌产品的轧盖作为洁净工艺在 A 级送风保护下进行时，应在轧盖前剔除无塞或跳塞的西林瓶作报废处理。应有经适当确认的自动化方法检测胶塞高度。

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

如果轧盖间需要人为干预，应使用适当的技术和组织性措施来防止人员直接接触西林瓶并最大程度减少污染。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.

逐个检查所有灌装后的注射产品容器是否存在外来污染物或其它缺陷。在确认过程中，根据风险和历史知识确定缺陷分类和关键程度。要考虑的因素包括但不限于缺陷对患者和给药途径的潜在影响。应对不同的缺陷类型进行分类，并分析批次性能。如有不符合常规缺陷数量（基于常规和趋势数据）的异常缺陷批次。应进行调查。应建立并维护缺陷库，录入所有已知类型的缺陷，并将其应用到生产和质量保证人员的培训中。在对已接受容器的后续取样和检查过程中，不应发现关键缺陷。随后发现的任何关键缺陷都应触发调查，因为它表明初始检查可能失败。

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.

人工检查时，应在有适当照明和环境的受控条件下进行。检查率应经适当控制和确认。执行检查的操作员应至少每年接受目检资质确认（如在正常情况下佩戴矫正镜片，则在接受资质确认时也应佩戴该镜片）。

应使用来自生产商缺陷库的适当样本进行资质确认，并考虑最差条件（例如，检查时间、传送产品给操作员的传送带系统的线速度、容器尺寸或疲劳程度），并且应包括对视力检查的考虑。应尽可能减少操作员的注意力分散，并应在检查时经常进行适当的休息。

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.

如果采用自动化检查方法，应对检查程序进行验证以发现已知缺陷（可能影响产品质量或安全性的缺陷），并且自动化检查应等同于或优于人工检查。应在设备启动之前使用代表性缺陷样品挑战设备的件能，并且在整个批次中定期进行。

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.

应记录检查结果，并对缺陷类型和数字进行趋势分析。还应根据统计学原则对各种缺陷类型的不合格率进行趋势分析。当观察到不良趋势时，应评估对市场上产品的影响，作为调查的一部分。

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.

在可能的情况下，成品应使用经验证且受控的灭菌工艺进行最终灭菌，因为这比经验证且受控的除菌过滤工艺和/或无菌工艺提供更大的无菌保证。当产品不能最终灭菌时，应考虑使用无菌工艺后最终热处理，结合无菌工艺，以提供更好的无菌保证。

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.

灭菌用设备和循环/程序的选择、设计及位置摆放应基于科学原则和能证明灭菌工艺可重复性、可靠性的数据。应定义所有参数，并在关键时对其进行控制、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.

所有灭菌工艺均应经过验证。验证研究应考虑产品组成、储存条件以及从待灭菌产品或物料的准备到其灭菌之间的最长时间。在采用任何灭菌工艺之前，应验证该工艺与其产品和设备的适用性，以及该工艺的效能（即每种类型的待处理负载的所有部分都始终达到预期的灭菌条件），验证应主要通过物理测定，在适当情况下通过生物指示剂（BI）。对于有效的灭菌，产品以及表面和组分的表面都应进行必要的处理，处理过程应经过设计以确保达到要求。

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.

若采用的产品灭菌方法未纳入现行药典，或灭菌方法用于非简单的水溶液，应特别注意。应尽可能首选加热灭菌方法。

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.

所有灭菌工艺都应建立经验证的装载模式，并且装载模式应定期进行再验证。最大装载和最小装载也应视为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.

根据风险按照预定的时间间隔审核和确认灭菌工艺的有效性。对于被认为是最差条件的装载模式，应至少每年一次定期开展加热灭菌周期的再验证。其它装载模式应以 CCS 中论证的频率进行验证。

8.40 Routine operating parameters should be established and adhered to for all sterilisation processes, e.g. physical parameters and loading patterns.

所有灭菌工艺都应确定建立常规运行参数（例如物理参数和装载模式）并照此执行。

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.

应建立适当机制，发现不符合验证参数的灭菌循环。应对任何失败的灭菌或不符合经验证工艺过程的灭菌（例如加热循环等阶段较长或较短）进行调查。

8.42 Suitable Bls 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.

在适当位置放置合适的 BI 可作为支持灭菌工艺验证的附加方法。应按照生产商的说明贮存和使用 BI。使用 BI 支持验证和/或监测灭菌工艺（例如环氧乙烷灭菌）时，灭菌循环均应进行阳性对照检测。如果使用了 BI，应采取严格的预防措施，避免使微生物污染转移至生产或其它检测过程。不能仅靠 BI 结果推翻其它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。供应商应经过资质确认，并控制运输和储存条件，避免影响 BI 质量。使用新一批 BI 前，应确认该批次的指示微生物的种群、纯度和特性。对于 D 值、Z 值等其它关键参数，通常可以参考由合格供应商提供的批证书。

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.

应制定明确的方法区分未灭菌和已灭菌的产品、设备和组件。用于运载产品、其它设备和/或组件的用具（如篮子或托盘）应清晰地标明（或具电子追踪）产品名称、批号及灭菌状态。在适当的情况下，可以使用指示剂（如高压灭菌指示胶带或辐照灭菌指示剂）来指示某批次（或子批物料、组件、设备）是否已经过灭菌处理。但这些指示剂仅表示有无灭菌处理，并不代表产品处于无菌状态或已达到要求的无菌保证水平。

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.

每次灭菌应有记录。每个灭菌循环应具有唯一的标识符。其符合情况应作为批认证/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.

如有要求，应对物料、设备和组件进行灭菌，所用灭菌方法应适用于相应物料，并经过验证。灭菌后应采取适当的保护措施，防止再次污染。如果灭菌后的物品未在灭菌后立即使用，则应采用适当密封的包装贮存，并应确定最长保持时间。在合理情况下，如果组件被包装在多层无菌包装中，且无菌包装的完整性和构造便于操作人员在将其转移至 A 级时即时消毒（例如，使用多层无菌包装，每次从较低级别区转移至较高级别区时去除一层包装），则这样包装的组件不需要存放在洁净室中。如果在密封包装中进行密闭防护，则应在灭菌前进行包装。

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.

如果物料、设备、组件和辅助用品在密封包装中灭菌，然后转入 A 级区，则应使用经验证的适当方法（例如气锁或传递窗），同时对密封包装的外部进行消毒。还应考虑使用快速传送接口技术。应证明这些方法能够有效控制 A 级和 B 级区的潜在污染风险。同样，应证明消毒方法能够将包装上的任何污染有效减少至进入 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.

如果物料、设备、组分和辅助用品在密封包装或容器中灭菌，包装应经过确认，以最大限度减少微粒、微生物、内毒素/热原或化学污染的风险，并与所选灭菌方法相容。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、灭菌前的最长保持时间以及被灭菌物品的最长有效期。应在使用前检查每种被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.

对于不直接或间接接触产品，并且是无菌工艺所必需但不能灭菌的物料、设备、组件和辅助用品，应建立有效且经验证的消毒和转移工艺。消毒后应采取保护措施，防止物品再次污染。这些物品以及代表潜在污染途径的其它因素应包含在环境监测计划中。

Sterilisation by heat

加热灭菌

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).

应使用有适当准确度和精确度的设备，以电子或纸质形式记录每个加热灭菌循环。系统的控制和监测仪器中应有保障措施和/或冗余，以检测不符合已验证参数的循环，并中止该循坏或判定该循环失败（例如，通过使用连接到独立控制和监测系统的双设备/双探头）。

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过程中确定，并根据系统设计进行选择, 以正确记录和反映常规循环条件。验证研究的设计应证明系统控制和记录探头位置的适用性，并应包括在验证过程中使用位于同一位置的独立监测探头来确认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.

在灭菌时间段起始测量之前，整个负载应达到所需温度。对于在负载内使用参照探头控制的灭菌循环，应特别注意，负载探头温度在循环开始前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.

在加热灭菌循环的高温阶段结束后，应采取预防措施防止已灭菌负载在冷却过程中被污染。与产品或已灭菌物料接触的任何冷却液体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.

在已批准参数放行的情况下，产品生命周期验证和生产工艺的日常监测应采用稳健的系统。该系统应定期回顾。关于参数放行的更多指导见附录 17。

Moist heat sterilisation

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).

湿热灭菌可以利用蒸汽（直接或间接接触）实现，也可以包括其它系统，如过热水系统（喷淋或浸没循环），可用于可能被其他循环设计损坏的容器（例如吹灌封容器、塑料袋等）。

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，待灭菌的物品应干燥，并用能排气和蒸汽穿透且能防止灭菌后再次污染的保护屏障系统进行包装。从灭菌柜中取出时，所有装载的物品应干燥。负载干燥度应通过目检确认，作为灭菌工艺验收的一部分。

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.

对于多孔循环（硬物）来说，应监测灭菌过程的时间、温度和压力，并进行记录。每个已灭菌物品从高压灭菌釜中取出时，检查其完整性、包装材料完整性及湿度。任何不符合预期的物品均应移出生产区并进行调查。

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.

对于能够进行预真空灭菌循环的高压灭菌釜，应在整个灭菌过程中记录腔室排水口的温度。在适当的情况下，也可以使用负载探头，但控制系统应仍与负载验证相关联。对于在线蒸汽灭菌系统，应记录适当的冷凝水排放点在灭菌全过程中的温度。

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 Fo. 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.

多孔循环的验证应包括计算平衡时间、暴露时间、压力与温度的相关性以及暴露期间的最小/最大温度范围。液体循环的验证应包括温度，时间和/或 F_0。关键操作参数应符合规定的限度（包括适当的公差），并作为灭菌验证和常规循环可接受标准的一部分予以确认。

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.

当真空阶段是循环的一部分或系统在灭菌后返回到低于灭菌柜环境的压力时，应定期（通常为每周）进行灭菌柜的泄漏测试。

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.

当灭菌工艺包括气洗（例如多孔高压灭菌釜负载、冻干机室）时，应充分保证灭菌前和灭菌过程中排气。对于高压灭菌釜，应包括排气测试（通常每天进行）或空气探测器系统的使用。待灭菌的负载应经过设计以支持有效排气和自由排水，以防止凝结水的积聚。

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).

应通过适当的循环设计和控制（例如，设置正确的压力，加热和冷却速率以及装载模式），防止最终灭菌的非刚性容器（例如采用吹灌封或者成型-灌装-密封技术生产的容器）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.

当采用在线蒸汽灭菌系统进行灭菌时（例如，对于固定管道系统，容器和冻干机箱体），系统应经过适当的设计和验证，确保系统的所有部分都能经受所需的处理。应在日常使用中监测系统适当位置的温度、压力和时间，确保所有部分都经过有效和可重复的灭菌。初始和例行验证中应证明这些位置能代表升温最慢的位置并与之相关。一旦系统经过在线蒸汽灭菌，应保持完整，并在操作需要时在使用前放置在正压下或配备除菌排气过滤器。

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液体负载循环中，热水应始终到达所有要求的接触点。初始确认研究应包括整个负载的温度映射。应对设备进行例行检查以确保喷嘴（水被引入的地方）没有堵塞，排水管没有碎屑。

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.

过热水高压灭菌釜中液体负载的灭菌验证应包括整个负载的温度映射以及热穿透和重现性研究。负载的所有部分应均匀加热并在指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条件相关联。

Dry heat sterilisation

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力去除难以消除的热稳定性污染物（如内毒素/热原），通常用于无菌灌装组件的准备。当在既定限度内常规操作时，产品、组件或设备所暴露的时间和温度的组合应当能够产生充分且可重复的致死率和/或内毒素/热原灭活/去除。该工艺可以在烘箱或连续隧道工艺过程中进行，例如用于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/除热原隧道烘箱的配置应能通过保持适当的压差以及经由隧道的气流来保护 A 级灭菌区的完整性和性能。应评估空气压差曲线。应评估任何气流变化的影响，以确保维持加热曲线。提供给隧道的所有

空气应通过至少一个 HEPA 过滤器，并应至少每半年检测一次，以证明空气过滤器的完整性。与灭菌后组件接触的任何隧道烘箱部件应进行适当的灭菌或消毒。在验证和/或日常加工中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.

最低温度和最高温度。

iii. Heat penetration of the material/article.

物料/物品的热渗透。

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.

通过与热分布和热渗透研究相关的空气压差曲线确定的气流。

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.

当使用热处理作为任何组分或产品接触设备/物料的除热原工艺的一部分时，应进行验证研究以证明该工艺能提供合适的 F_h 值，并使内毒素浓度至少降低 3 个对数值。当达到这一要求时，在这些情况下不需要证明灭菌。

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.

在验证中应使用加有内毒素的容器，并应对容器进行全面的物料平衡管理。容器应能代表通常生产的物料（涉及包装材料的组成、孔隙率、尺寸、标称容积）。还应证明内毒素的定量值和回收率。

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:

干热烘箱通常用于对内包装组分、原辅料或原料药进行灭菌或除热原，但也可用于其它工艺过程。除非能保持包装的完整性，否则在整个灭菌和灭菌后放置过程中，干热烘箱应保持相对于较低级别洁净区的正压。所有进入烘箱的空气应通过 HEPA 过滤器。在确认和/或日常加工时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.

暴露期/时间。

iii. Chamber pressure (for maintenance of over pressure).

腔室压力（用于维持过压）。

iv. Air speed.

风速。

v. Air quality within the oven.

烘箱内的空气质量。

vi. Heat penetration of material/article (slow to heat spots).

物料/物品的热穿透（冷点）。

vii. Heat distribution/uniformity.

热分布/均匀性。

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，包括最小装载和最大装载。

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。紫外线照射不是可接受的灭菌方法。关于电离辐照灭菌的指导见附录 12。

8.72 Validation procedures should ensure that the effects of variation in density of the product and packages are considered.

验证规程应确保考虑了产品密度和包装的变化的影响。

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.

此方法仅在无其它可行方法时使用。在工艺验证期间，应证明环氧乙烷对产品没有破坏性影响，并证明脱气条件和时间足够将任何残留的环氧乙烷（EO）气体和反应产物减少至该产品/物料规定的可接受限度内。

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必不可少的，应采取预防措施以避免存在可能被包裹在晶体或干蛋白等物质中的微生物。包装材料的性质、孔隙率和数量会显著影响工艺。

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.

在接触气体之前，物料应与工艺所需的湿度和温度达到平衡。当使用蒸汽作为负载的灭菌条件时，蒸汽应具有适当的质量。这一过程所需时间应与其相反需求（尽量减少灭菌前时间）结合考虑取平衡。

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合适的 BI 进行监测，测试单元数量适当、分布于负载的确定位置（验证研究中已被证明是最差条件的位置）。

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:

可考虑作为灭菌工艺验证和常规监测一部分的关键工艺参数，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.

使用的 EO 气体量。

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.

灭菌后，负载应进行空气置换，以使 EO 气体和/或其反应产物从包装产品中解吸至预定水平。换气可以发生在灭菌室内和/或单独的换气室或换气区内。换气阶段应作为整体 EO 灭菌工艺验证的一部分进行验证。

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 iscompatible 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灭菌，溶液或液体应通过除菌级过滤器（标称孔径最大 0.22um,经过适当验证能获得无菌滤液）进行灭菌，然后无菌灌装到预先灭菌的容器中。所用过滤器应确保与产品相容并符合上市许可（参见第 8.135 节）。

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.

可在生产工艺过程中，多个点使用预过滤器和/或除菌级过滤器，以确保液体在经过最终除菌过滤器之前生物负载低且受控。由于除菌过滤工艺相比于其它灭菌工艺具有潜在的额外风险，应考虑尽可能靠近灌装点通过除菌级过滤器进行额外过滤，作为整体 CCS 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).

过滤系统组分的选择及其在过滤系统内的相互连接和布置，包括预过滤器，应基于产品的关键质量属性，并经过论证和记录。过滤系统应最大限度地减少纤维和微粒的产生，不引起或导致不可接受的杂质水平，不具有改变产品质量和效果的特性。同样，过滤器的性质应与流体相容，不受待过滤产品的不利影响。应评估产品成分的吸附和过滤器组分的提取/浸出（参见 8.135 节）。

8.82 The filtration system should be designed to:

过滤系统应设计为：

i. Allow operation within validated process parameters.

允许在经验证的工艺参数内操作。

ii. Maintain the sterility of the filtrate.

保持滤液的无菌性。

iii. Minimize the number of aseptic connections required between the final sterilising grade filter and the final filling of the product.

最大程度地减少最终除菌级过滤器和最终灌装之间所需的无菌连接次数。

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.

允许在必要时进行灭菌程序，包括在线灭菌。

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.

允许在必要时进行过滤前后 0.22μm 最终除菌级过滤器的在线完整性测试，优选作为密闭系统。应选择在线完整性测试方法以避免对产品质量的任何不良影响。

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.

液体的除菌过滤应按照相关药典要求进行验证。验证可以根据产品的不同规格或变量进行分组，但应在最差条件下进行。分组的基本原理应经过论证并用文件记录。

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.

在过滤器验证过程中，应尽可能使用待过滤产品进行除菌级过滤器的细菌截留测试。如果待过滤产品不适合用于细菌截留测试，应论证合适的替代产品的合理性。应论证用于细菌截留试验的挑战微生物的合理性。

8.85 Filtration parameters that should be considered and established during validation should include, but are not limited to:

应在验证过程中考虑并确定的过滤参数，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.

应基于过滤器生产商的建议或待过滤液体。应建立适用的完整性测试值标准。

• 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.

如果系统冲洗或在线完整性测试使用的液体不是该产品，应采取适当措施避以免对产品质量的任何有害影响。

ii. Filtration process conditions including:

过滤工艺条件包括：

• Fluid pre-filtration holding time and effect on bioburden.

液体预过滤保持时间和对生物负载的影响。

• Filter conditioning, with fluid if necessary.

必要时使用液体预处理过滤器。

• Maximum filtration time/total time filter is in contact with the fluid.

最长过滤时间/过滤器与液体的总接触时间。

• Maximum operating pressure.

最大工作压力。

• Flow rate.

流速。

• Maximum filtration volume.

最大过滤体积。

• Temperature.

温度。

• The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.

过滤已知体积的待包装溶液所需时间以及过滤器上的压差。

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.

应实施常规工艺控制以确保符合经验证的过滤参数。关键工艺参数的结果应包含在批记录中，包括但不限于过滤已知体积的待包装溶液所需的最短时间和过滤器两端的压差。生产过程中与关键参数的任何显着差异都应记录并调查。

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:

应在使用前通过完整性测试（使用前灭菌后完整性测试或 PUPSIT）核实无菌过滤器组件的完整性，检查由于过滤器使用前准备造成的损坏和完整性降低。用于液体除菌的除菌级过滤器，应在使用后进行非破坏性的完整性测试，然后再将滤器从外壳中取出。完整性测试过程应经过验证，测试结果应与验证过程中确定的过滤器的微生物截留能力相关联。所使用的测试例子包括起泡点、扩散流、水侵入法或压力保持测试。已认识到，由于工艺限制（例如过滤非常少量的溶液），PUPSIT 并不总是在灭菌后进行。在这些情况下，可以采取替代方法，前提是已经进行了全面的风险评估，并且通过采取适当的控制来降低非无菌性的风险，从而实现合规。风险评估中要考虑的要点应包括但不限于：

i. In depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized.

深入了解知识并控制过滤除菌工艺，以确保最大程度降低损坏过滤器的可能性。

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

深入了解知识并控制供应链，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.

无菌过滤器的包装，以防止在运输和储有过程中损坏过滤器。

iii. In depth process knowledge such as:

深入了解工艺知识，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,包括微粒物水平以及是否存在影响过滤器完整性的任何风险, 例如可能改变完整性测试值从而妨碍在使用后过滤器完整性测试中检出非完整的过滤器。

• 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之前的预过滤和处理步骤，这些步骤去除微粒物并使产品在除菌过滤前变澄清。

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.

关键无菌气体和空气的排气过滤器（与产品的无菌性直接相关）的完整性应通过使用后测试进行核实，过滤器留在过滤器组分或壳体中。

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).

非关键空气或气体的排气过滤器的完整性应以适当的时间间隔予以确认和记录。如果气体过滤器需长时间放置，应在安装时和更换之前进行完整性测试。应基于风险规定最长使用时间并进行监测（例如考虑最大使用次数和允许的热处理/灭菌循环，如适用）。

8.90 For gas filtration, unintended moistening or wetting of the filter or filter equipment should be avoided.

对于气体过滤，应避免过滤器或过滤设备意外润湿或弄湿。

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.

如果除菌过滤工艺已作为多个过滤器组成的单个系统经过验证，能保证给定液体的无菌性，则该过滤系统被认为是单个灭菌单元，系统内的所有过滤器应在使用后通过完整性测试。

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 postuse 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.

对于冗余过滤系统（存在第二个冗余除菌级过滤器作为备用过滤器，但灭菌工艺验证时仅用一个过滤器），应进行主要除菌级过滤器的使用后完整性测试，如果证明是完整的，那么冗余（备用）过滤器的使用后完整性测试不是必需的。但如果主过滤器的使用后完整性测试失败，应对二级（冗余）过滤器进行使用后完整性测试，同时进行调查和风险评估，确定主过滤器测试失败的原因。

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.

生物负载样品应取自待包装产品，并在最终除菌过滤前即时取样。如果使用冗余过滤装置，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.

液体除菌级过滤器应在单个批次加工后丢弃，同一过滤器不应连续使用超过一个工作日，除非此类使用经过验证。

8.95 Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:

如果产品的阶段式生产在 CCS 中经过适当论证并经过验证，过滤器使用者应：

i. Assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid.

评估并记录与给定液体除菌过滤工艺中过滤器的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，以证明给定液体和给定除菌过滤工艺中过滤器的使用时间不会影响最终除菌级过滤器的性能或滤液质量。

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，并采取控制以确保过滤器的使用不会超出了经过验证的最长持续时间。应保存这些控制措施的记录。

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.

采取控制以确保不使用被液体或清洁剂残留物污染的过滤器，或被认为有缺陷的过滤器。

Form-Fill-Seal (FFS)

成型-灌装-密封（FFS）

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 机器的条件应符合本附录第 8.3 和 8.4 节的环境要求。无菌生产中使用的 FFS 机器的条件应符合本附录第 8.10 节的环境要求。

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.

在组件装配、供应和处理过程中，应通过适当的控制将 FFS 工艺中使用的包装膜的污染降至最低。由于包装膜的关键性，应实施规程以确保提供的膜符合规定的质量标准并且具有适当的质量，包括材料的厚度和强度、微生物和微粒污染、完整性和图案（如相关）。应在 PQS 中定义和控制包装膜和相关组分的取样频率、生物负载以及内毒素/热原水平（如适用），并在 CCS 中予以考虑。

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，包括安装、灌装、密封和切割工艺，以便对关键工艺参数进行适当的了解、验证、控制和监测。

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表层通气）应在尽可能靠近使用点的位置进行适当过滤。所用气体的质量和气体过滤系统的有效性应按照第 6.18 和 6.19 节进行定期确认。

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 确认过程中确定的控制措施应与 CCS 保持一致。应考虑的方面包括但不限于：

i. Determination of the boundaries of the critical zone.

关键区边界的确定。

ii. Environmental control and monitoring, both of the machine and the background in which it is placed.

环境控制和监测，包括机器及其背景区的环境。

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.

批次或灌装阶段的持续时间。

vi. Control of packaging films, including any requirements for film decontamination or sterilisation.

包装膜的控制，包括对膜净化或灭菌的任何要求。

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）。

8.101 Critical process parameters for FFS should be determined during equipment qualification and should include, but are not limited to:

应在设备确认过程中确定 FFS 的关键工艺参数，包括但不限于：

i. Settings for uniform package dimensions and cutting in accordance with validated parameters.

根据经验证的参数进行统一的包装尺寸和裁切设置。

ii. Setting, maintenance and monitoring of validated forming temperatures (including preheating and cooling), forming times and pressures as relevant.

经验证的成型温度（包括预热和冷却）、成型时间和压力的设置、维护和监测（如相关）。

iii. Setting, maintenance and monitoring of validated sealing temperatures, sealing temperatureuniformity across the seal, sealing times and pressures as relevant.

经验证的封口温度、整个封口的封口温度均匀性、封口时间和压力的设置、维护和监测（如相关）。

iv. Environmental and product temperature.

环境和产品温度。

v. Batch-specific testing of package seal strength and uniformity.

具体批次的包装密封强度和均匀性检验。

vi. Settings for correct filling volumes, speeds and uniformity.

设置正确的装量、速度和均一性。

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（批编码）、压花或凹刻的设置，以确保单元完整性不受影响。

viii. Methods and parameters for integrity testing of filled containers (see paragraph 8.22).

已灌装容器完整性测试的方法和参数（参见第 8.22 节）。

8.102 Appropriate procedures for the verification, monitoring and recording of FFS critical process parameters and equipment operation should be applied during production.

生产过程中应采用适当的规程来确认、监测和记录 FFS 关键工艺参数和设备运行情况。

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.

操作规程应描述如何检测和纠正成型和密封问题。应记录和调查不合格单元或密封问题。

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.

应根据风险建立适当的维护规程，并包括对单元密封有效性至关重要的工具的维护和检查计划。发现的任何表明存在潜在产品质量问题的问题都应记录并进行调查。

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装设备应至少安装在 D 级环境中。灌装点的条件应符合第 8.3 和 8.4 节的环境要求。

8.106 BFS used for aseptic processing:

无菌工艺所用的 BFS：

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.

对于用于无菌灌装的往复式设备，型坯在环境中敞口，因此进行型坯挤出、吹塑和密封的关键区域应符合 A 级条件。灌装环境应进行设计和维护，从而在静态和动态下均符合活性粒子和总微粒限度的 A 级条件。

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，型坯通常在成型后密闭于环境，型坯内的灌装环境应进行设计和维护，从而在静态和动态下均符合活性粒子和总微粒限度的 A 级条件。

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 级工作服，设备应至少安装在 C 级环境中。在 C 级区穿着 A/B 级工作服的操作人员的微生物监测应按照风险管理原则进行，所采用的限度和监测频率应考虑这些操作人员执行的活动。

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.

由于操作过程中聚合物挤出和切割产生的微粒，以及 BFS 设备关键灌装区的尺寸限制，预计不会对 BFS 设备的总微粒进行动态监测。但是，应有数据证明设备的设计可确保灌装工艺环境的关键区域在动态下满足 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 工艺的活性粒子环境监测应基于风险，并按照本附录第 9 节进行设计。应在关键操作的全过程中（包括设备组装）进行动态活性粒子监测。对于旋转式 BFS 设备，众所周知，可能无法监测关键灌装区域。

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气流通路以及工艺的高热输出的影响，（例如，通过使用气流可视化研究和/或其它等同研究）。环境监测计划还应考虑诸如空气过滤器配置、空气过滤器完整性、冷却系统完整性（参见第 6.21 节）、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，接触容器关键表面的空气或其它气体应进行适当的过滤。所用气体的质量和气体过滤系统的有效性应按照第 6.18 和 6.19 节进行定期确认。

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.

应通过适当设计、控制和维护聚合物颗粒储存、取样和分配系统，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的无菌保证的能力。应在 PQS 中定义和控制聚合物原材料的取样频率、生物负载以及内毒素/热原水平（如适用），并在 CCS 中予以考虑。

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、模塑和密封，以及必要时灌装机再灭菌的干预措施，应在灌装规程中明确规定和描述，并包括在 APS 中（如相关）（参见第 9.34、9.35 和 9.36 节）。

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 确认过程中确定的控制措施应与工厂的 CCS 保持一致。应考虑的方面包括但不限于：

i. Determination of the boundaries of the critical zone.

关键区边界的确定。

ii. Environmental control and monitoring, both of the machine and the background in which it is placed.

环境控制和监测，包括设备及其环境。

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.

批次或灌装阶段的持续时间。

vi. Control of polymer granulate, including distribution systems and critical extrusion temperatures.

聚合物颗粒的控制，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:

应在设备确认过程中确定 BFS 的关键工艺参数，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（芯棒）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、维护和监测，包括温度、速度和型坯厚度的挤出机喉部设置。

iii. Setting, maintenance and monitoring of mould temperatures, including rate of cooling where necessary for product stability.

模具温度的设置、维护和监测，包括产品稳定性所需的冷却速率。

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

添加到成型单元中的辅助组分的准备和灭菌，例如瓶盖。

v. Environmental control, cleaning, sterilisation and monitoring of the critical extrusion, transfer and filling areas as relevant.

关键挤压区、转移区和灌装区的环境控制、清洁、灭菌和监测（如相关）。

vi. Batch-specific testing of package wall-thickness at critical points of the container.

具体批次的容器关键点包装壁厚度检验。

vii. Settings for correct filling volumes, speeds and uniformity.

正确的装量、速度和均一性的设置。

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（批编码）、压花或凹刻的设置，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).

所有已灌装容器 100%完整性测试的方法和参数（参见第 8.22 节）。

x. Settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).

用于去除已灌装单元周围的废塑料的切割机或冲压机的设置（毛边去除）。

8.116 Appropriate procedures for the verification, monitoring and recording of BFS critical process parameters and equipment operation should be applied during production.

生产过程中应采用适当的规程来确认、监测和记录 BFS 关键工艺参数和设备运行情况。

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.

操作规程应描述如何检测和纠正吹塑、成型和密封问题。应记录和调查不合格单元或密封问题。

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分（例如，向 LVP 瓶添加瓶盖），这些组分应适当净化并使用清洁、受控的工艺添加到工艺过程中。

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，添加组分应在 A 级条件下进行，以确保关键表面的无菌性，并使用预灭菌的组分。

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.

对于最终灭菌产品，最终灭菌工艺的验证应确保组分和成型容器之间的所有关键产品通路的无菌性，包括灭菌过程中未润湿的区域。

iii. Testing procedures should be established and validated to ensure the effective sealing of components and moulded containers.

应建立并验证检验规程，以确保组分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.

应根据风险建立适当的维护规程，并包括对单元密封、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被认为是关键设备，任何对模具的变更或修改都应触发对成品容器完整性的评估，并在评估表明的情况下，应有验证支持。发现的任何表明存在潜在产品质量问题的问题都应记录并进行调查。

Lyophilization

冻干

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.

冷冻干燥是一个非常关键的工艺步骤，所有影响产品或物料无菌性的活动均应认为是对已灭菌产品的无菌工艺。冻干设备及其工艺均应当设计以保证产品或物料的无菌性，防止在产品灌装到冻干完成之间的微生物或微粒污染。应在工厂的 CCS 中确定所有在线控制措施。

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、西林瓶支撑环）的灭菌应经过验证，应在 APS 期间适当挑战灭菌循环和使用之间的保持时间（参见第 9.33 节）。冻干机应根据系统设计定期灭菌。应在维护或清洁后进行再灭菌。灭菌后的冻干机和相关设备应受到保护，避免污染。

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.

冻干机和相关产品转移和装载/卸载区域应经过设计，尽可能减少操作人员的干预。冻干机灭菌的频率应根据设计和使用过程中与系统污染相关的风险来确定。没有屏障技术隔离的手动装载或卸载的冻干机应在每次装载前进行灭菌。对于通过自动化系统装载和卸载或由密闭的屏障系统保护的冻干机，应论证并记录其灭菌频率，作为 CCS 的一部分。

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.

灭菌后和冻干过程中应保持冻干机的完整性。用于维持冻干机完整性的过滤器应在系统每次使用前进行灭菌，其完整性测试结果应作为批次认证/放行的一部分。应记录冻干室的真空/检漏测试的频率，应规定最大允许的空气泄漏，并在每个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.

应定期检查冻干托盘以确保其没有变形或损坏。

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）的设计要点，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).

应始终在 A 级条件下将半封闭容器转移到冻干机中，转移方式应旨在最大程度减少操作员的直接干预。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，以确保维持用于转移部分密闭容器的系统的洁净度。或者，在经过验证的情况下，在 A 级密封且在 B 级区时不再重新打开的托盘可用于保护半加塞的西林瓶（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.

转移装置和装载区的通风不应对气流模式造成不良影响。

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（例如半加塞的西林瓶）应在 A 级条件下，并且通常应通过物理屏障技术或任何其它适用措施与操作员隔开。

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 duringsubsequent handling.

在冻干机打升前，产品处十小完全加塞状态的，产品移出冻干机进行下一步操作的过程中应维持在 A 级环境下。

vi. Utensils used during loading and unloading of the lyophilizer (e.g. trays, bags, placing devices, tweezers) should be sterile.

冻干机装载和卸载过程中使用的器具（例如托盘、袋子、定位装置、镶子）应为无菌状态。

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.

密闭系统的使用可降低邻近环境中微生物、微粒和化学污染的风险。密闭系统应始终设计为减少人工操作的需求和相关风险。

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).

确保无菌工艺中密闭系统的所有产品接触表面的无菌性至关重要。无菌工艺中任何密闭系统的设计和选择应确保维持无菌性。最终除菌级过滤器之后，无菌设备（例如管道/管道系统）与已灭菌产品通路的连接应设计成无菌连接（例如通过固有无菌连接装置）。

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.

应采取适当的措施确保无菌连接所用组分的完整性。应在 CCS 中确定并记录实现方式。如果存在影响产品无菌性的风险，应考虑适当的系统完整性测试。供应商评价应包括收集整理与可能导致系统丧失无菌性的潜在失效模式相关的数据。

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).

密闭系统所处的环境应基于其设计和所采取的工艺。对于无菌工艺，如果存在系统完整性可能受到影响的任何风险，系统应位于 A 级。如果证明系统每次使用时都保持完整性（例如通过压力测试和/或监测），那么可以使用较低级别区。应彻底评估分级区域之间的任何转移（参见第 4.10 节）。如果需开启密闭系统（例如生产线的维护），则应在适合于物料的分级区域内进行（例如，最终灭菌工艺的 C 级，或无菌工艺的 A 级）或进行进一步清洁和消毒（以及灭菌（针对无菌工艺））。

Single use systems (SUS)

一次性系统（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.

一次性系统（SUS）是指在无菌产品生产中运用、代替可重复使用设备的技术。SUS 可以是单独的组分，也可以由多个组分组成，如袋子、过滤器、管道、连接器、阀门、储瓶及传感器等。一次性系统应设计为减少对操作的需求以及降低人工干预的复杂性。

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:

有一些与 SUS 有关的特定风险，应作为 CCS 的一部分予以评估。这些风险包括但不限于：

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之间的相互作用（例如吸附，或浸出物&提取物）。

ii. The fragile nature of the system compared with fixed reusable systems.

与固定的可重复使用的系统相比的脆弱性。

iii. The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made.

手动操作（包括系统的检查和处理）和连接的数量及复杂性增加。

iv. The complexity of the assembly.

装配的复杂性。

v. The performance of the pre- and post-use integrity testing for sterilising grade filters (see paragraph 8.87).

除菌级过滤器的使用前后完整性测试的性能（参见第 8.87 节）。

vi. The risk of holes and leakage.

存在孔洞和泄漏的风险。

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

打开外包装时损害系统的可能性。

viii. The risk of particle contamination.

微粒污染风险。

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，证明对系统性能无不良影响。

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.

一次性系统（包括灭菌）供应商的评估对于这些系统的选择和使用至关重要。对于无菌 SUS，应进行无菌保证确认，作为供应商资质确认的一部分，并且在接收时应检查每个单元的灭菌证据。

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与产品接触表面的吸附性和反应性。

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.

应评估 SUS 的提取和浸出概况以及对产品质量的任何影响，特别是当系统由聚合物材料制成时。应针对每个组分评估可提取物概况数据的适用性。对于被认为具有高浸出风险的组分，包括那些可能吸收已加工物料的组分或有较长的物料接触时间的组分，应考虑对其可浸出概况研究进行评估，包括安全性问题。如果模拟工艺条件，应准确反映实际工艺条件并基于科学依据。

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 的设计应能在预期操作条件和持续时间内保持完整性。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，有必要注意一次性组分的结构完整性。这应包括确认固有无菌连接装置（热密封和机械密封）在这些条件下保持完整。

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.

应建立并执行 SUS 可接受标准，可接受标准应与产品和工艺的风险或关键性相应。接收时，应对每件 SUS 进行检查以确保其按照已批准的质量标准生产、供应和交付。外包装（例如外包装盒、产品袋的外观）、标签印刷的目检，以及所附文件（例如，合格证书和灭菌证明）的审核，应在使用前进行并用文件记录。

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

8.139 SUS 的关键人工处理操作，如装配和连接，应该采取适当的控制措施，并应在 APS 中确认。

9 Environmental & process monitoring 环境监测和工艺监测

General

总则

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.

场地的环境监测和工艺监测计划构成整个 CCS 的一部分，用于监测旨在最大程度降低微生物和微粒污染风险的控制措施。应注意，监测系统的每个要素（活性粒子，非活性粒子和 APS）的可靠性在单独来看时是有限的，不应单独视为无菌的指标。当综合考虑时，这些结果有助于确认所监测系统的设计、验证和操作的可靠性。

9.2 This programme is typically comprised of the following elements:

本计划通常包括以下内容：

i. Environmental monitoring - total particle.

环境监测——总微粒。

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、相对湿度和其它具体特性。

iv. APS (aseptically manufactured product only).

APS（仅用于无菌生产的产品）。

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.

应将来自这些系统的信息用于常规批次认证/放行以及工艺回顾或调查期间的定期评估。这适用于最终灭菌和无菌工艺，但影响的关键程度可能因产品和工艺类型的不同而不同。

Environmental and process monitoring

环境监测和工艺监测

9.4 An environmental monitoring programme should be established and documented. The purpose of the environmental monitoring programme, is to:

应制订并记录环境监测计划。环境监测计划的目的是：

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.

根据设计和法规要求，保证洁净室和洁净空气设备持续提供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.

ii. 有效地检测偏离环境限度的情况，触发调查和产品质量风险评估。

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).

应进行风险评估，建立全面的环境监测计划，包括取样位置、监测频率、监测方法和培养条件（如时间、温度、需氧和/或厌氧条件）。

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.

这些风险评估应基于对工艺输入和最终产品、设施、设备、具体工艺和步骤的关键性、所涉及的操作、常规监测数据、确认期间获得的监测数据的详细知识，以及对环境中分离的典型微生物菌群的知识。

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.

风险评估应包括确定关键监测位置，这些位置在加工过程中出现微生物可能会对产品质量产生影响（例如 A 级，无菌工艺区以及与 A 级区直接接触的 B 级区）。还应包括对空气可视化研究等其他信息的考虑。这些风险评估应定期回顾，以确认工厂环境监测计划的有效性。监测计划应在趋势分析和场地的 CCS 中予以考虑。

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.

所有加工的关键阶段（包括设备安装）都应对动态下洁净室、洁净空气设备和人员进行常规监测。

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).

温度和相对湿度等特性应控制在符合产品/工艺/人员要求的范围内，并应能够用于维护规定的洁净标准（例如 A 级或 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 级的监测应证明在关键操作中都维持了无菌工艺条件。监测位置应为对无菌设备表面、容器、密封件和产品造成最高污染风险的位置。监测位置的选择以及取样装置的定位和放置应证明合理，适合从关键区域获取可靠的数据。

9.8 Sampling methods should not pose a risk of contamination to the manufacturing operations.

采样方法不应给生产操作带来污染风险。

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.

对活性粒子和总微粒监测的结果应设置适当的警戒限和行动限。最大总微粒行动限见表 5，最大活性粒子行动限见表 6。然而，基于数据趋势分析、工艺性质或按照 CCS 中的规定，可以应用更严格的行动限。应根据洁净室确认测试的结果确定活性粒子和总微粒警戒限，并根据持续趋势数据定期回顾。

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（仅总微粒）、B 级、C 级和 D 级的警戒限，以便检出并解决不良趋势（例如指示环境控制恶化的数个事件或个别事件）。

9.11 Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:

监测规程应定义趋势分析方法。趋势分析应包括但不限于：

i. Increasing numbers of excursions from action limits or alert levels.

偏离行动限或警戒限的次数增加。

ii. Consecutive excursions from alert levels.

连续偏离警戒限。

iii. Regular but isolated excursion from action limits that may have a common cause, (e.g. single excursions that always follow planned preventative maintenance).

可能由共同原因引起的单独定期偏离行动限的事件（例如，经常在计划内预防性维护后出现的单次偏离）。

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.

微生物菌群类型和数量的变化以及特定微生物的优势。应特别注意回收到的可能表明失控、洁净度恶化的微生物或难以控制的微生物，例如可形成孢子的微生物和霉菌。

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.

动态下 C 级和 D 级洁净室的监测应基于确认期间收集的数据和常规数据，以便进行有效的趋势分析。警戒限和行动限的要求将取决于所执行操作的性质。行动限可能比表 5 和表 6 中列出的更为严格。

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.

9.13 如果超出行动限，操作规程应规定根本原因调查，对产品（包括在监测和报告之间生产的批次）潜在影响性的评估以及纠正和预防措施要求。如果超出警戒限，操作规程应规定评估和跟进，其中应包括对调查和/或纠正措施的考量，以避免环境的进一步恶化。

Environmental monitoring - total particle

环境监测——总微粒

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.

应建立总微粒监测计划，以获得数据用于评估潜在污染风险，并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.

表 5 给出了各级别环境监测的空气浮游微粒浓度限度。

Table 5: **Maximum permitted total particle concentration for monitoring.**

表 5：监测最大允许的总微粒浓度。

Grade 级别	**Maximum limits for total particle > 0.5 µm/m³** **> 0.5 µm/m³** 的微粒总数的最大限度 （每立方米）		**Maximum limits for total particle > 5 µm/m³** **> 5 µm/m³** 的微粒总数的最大限度 （每立方米）	
	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)] 未预先确定[(a)]	29 300	Not predetermined [(a)] 未预先确定[(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，动态限度未预先确定。生产商应根据风险评估和适用的常规数据建立动态限度。

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：操作完成后，在无人状态下经过确认期间确定的、短时间的“自净期”（指导值少于 20 分钟）后应达到表格中“静态”下的微粒限度（参见第 4.29 节）。

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、重叠损失等原因，偶尔出现 A 级中微粒计数值很大（特别是>5µm 的微粒），可被认为是假计数。但是，连续或定期的低水平计数可能表明存在污染事件，应进行调查。此类事件可能表明房间送风过滤系统开始失效、设备故障、机器组装和日常操作中不良行为的信号。

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

对于 A 级，应在关键操作的全过程中（包括设备组装）进行微粒监测。

9.17 The grade A area should be monitored continuously (for particles >0.5 and >5 μm) and with a suitable sample flow rate (at least 28 litres ($1ft^3$) per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.

A 级区应持续监测（30.5μm 和分的微粒）并采用合适的样本流速（每分钟至少 28 升（$1ft^3$））,以便捕获所有干扰、瞬态事件和任何系统恶化。系统应频繁关联每个单独样本的结果与警戒限和行动限，使得可以识别任何可能的偏移并及时做出响应。如果超出警戒限，应触发报警。规程应规定针对报警所采取的措施，包括考虑额外的微生物监测。

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.

建议对 B 级区使用类似的系统，采样频率可能降低。B 级区的监测频率和样本量应合适，以便程序能够捕获任何污染水平升高和系统恶化。如果超出警戒限，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、可能导致生物、化学或放射性危害的物料（例如涉及活微生物的物料，粉末物料或放射性物料）所带来的任何风险。

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.

如果由于所涉工艺而存在污染物，并且可能会损坏粒子计数器或造成危害（例如活微生物、粉末和辐射危害），所采用的监测频率和策略应确保风险前后的环境级别。应考虑增加活性粒子监测以确保对工艺的全面监测。另外，应对模拟操作进行监测。模拟操作应按适当的间隔进行，其方法应在 CCS 中有所规定。

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.

9.21 自动化系统所采的监测样本量通常是所用系统的采样速率的函数。样本量没有必要与洁净室和洁净空气设备的正式分级所用的样本量相同。应论证监测样本量的合理性。

Environmental and personnel monitoring - viable particle

环境和人员监测——活性粒子

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.

当进行无菌操作时，应采用多种方法经常进行微生物监测，例如沉降碟、定量空气采样、手套、洁净服和表面采样（例如棉签擦拭和接触碟）。应在 CCS 中论证所使用的采样方法的合理性，应证明不会对 A 级和 B 级的气流模式造成不利影响。在操作结束时应监测洁净室和设备表面。

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).

未进行正常生产操作的洁净室（例如，消毒后，生产开始前，批完成时和停产后）以及未使用的相关房间，也应进行活性粒子监测，以发现可能影响洁净室内控制的潜在污染事件。如果发生污染事件，可使用额外的采样位置以核实纠正措施（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.

在关键操作的全过程中，包括设备组装（无菌安装）和关键操作，应当对 A 级进行连续的空气活性粒子监测（例如空气采样或沉降碟）。对于 B 级洁净室，应基于对无菌工艺的影响风险，考虑类似的方式。监测方式应能捕获所有干扰、瞬态事件和任何系统恶化，并且避免由监测操作的干预引起的任何风险。

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.

风险评估应根据所执行的活动以及与关键区域的接近程度，对人员监测的位置、类型和频率进行评估。监测应包括在工艺过程中定期进行人员监测采样。人员监测采样应以不影响工艺过程的方式进行。对于人员监测，参与关键干预操作后（至少包括手套，但可能需要监测适用于工艺的洁净服区域）以及每次离开 B 级洁净室时（手套和洁净服），应特别考虑。如果在关键干预操作后监测手套，则应在继续活动之前更换外层手套。如果在关键干预操作后需要监测洁净服，则应在洁净室进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 级和 B 级区的人员进行微生物监测。当操作属于手动操作时（例如无菌配药或灌装），风险的增加应引起对洁净服微生物监测的重视，并在 CCS 中进行论证。

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).

如果是由生产人员例行监测，则应由质量部门进行定期监督（参见第 8.19 节）。

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.

生产商应考虑采用合适的替代监测系统（例如快速方法），以加速微生物污染问题的检出并降低对产品的风险。通过验证证明对已建立的方法具有等效性或优越性后，可以应用这些快速或自动微生物监测方法。

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.

应充分了解采样方法和所使用的设备，并应制订规程以便正确操作和解读所得结果。应当有所选采样方法的回收效率的支持性数据。

9.30 Action limits for viable particle contamination are shown in Table 6

表 6 列出了活性粒子污染的行动限

Table 6: **Maximum action limits for viable particle contamination**

表 6：活性粒子污染的最大行动限

Grade 级别	Air sample CFU/m^3 空气样品 CFU/m^3	Settle plates (diam. 90 mm) CFU/4 hours[a] 沉降碟（直径 90mm） CFU/4 小时[a]	Contact plates (diam. 55mm), CFU/plate[b] 接触碟（直径 55mm） CFU/碟[b]	Glove print, Including 5 fingers on both hands CFU/glove 手套印（包括双手的各 5 个手指） CFU/只
A A 级	No growth 无生长			
B B 级	10	5	5	5
C C 级	100	50	25	-
D D 级	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).

沉降碟应暴露在 A 级和 B 级区操作期间（包括设备安装），并在最多 4 小时后按要求更换（暴露时间应基于验证，包括回收研究，不应对所用培养基的适用性产生任何负面影响）。

- For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM.

-对于 C 级和 D 级区，暴露时间（最多 4 小时）和频率应基于 QRM。

- Individual settle plates may be exposed for less than 4 hours.

-单个沉降碟的暴露时间可以少于 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。C 级和 D 级区通常不需要进行常规工作服监测，具体取决于其功能。

[c] It should be noted that for grade A, any growth should result in an investigation.

应注意，A 级区域如有任何长菌情况都应进行调查。

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：应注意，上表中列出的监测方法类型是示例，可以使用其它方法，只要这些方法满足相同目的，即在整个关键工艺过程（产品可能被污染的过程，例如无菌生产线组装、无菌工艺、灌装和冻干机装载）中提供信息。

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：在整个文件中使用 CFU 表示限度。如果采用不同的或新的技术并且结果不以 CFU 的方式呈现，生产商应科学地论证其限度，并尽可能将其与 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.

应对 A 级和 B 级区检出的微生物进行鉴定，并应评估此类微生物对产品质量（每个相关批次）和整体受控状态的潜在影响。还应考虑对 C 级和 D 级区检出的微生物进行鉴定（例如，超出行动限或警戒限），或在分离出可能表明失控、洁净度恶化的微生物或难以控制的微生物（例如可形成孢子的微生物和霉菌）后进行鉴定，并定期充分更新对这些区域中典型菌群的认知。

Aseptic process simulation (APS) (also known as media fill)

无菌工艺模拟（APS）（又称培养基模拟灌装）

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.

无菌工艺中在线控制有效性的定期确认应包括使用无菌营养培养基和/或产品替代品的 APS——APS 不应被视为验证无菌工艺或无菌工艺方面的主要手段。无菌工艺的有效性应通过工艺设计、对药品质量体系和工艺控制的遵守情况、培训和监测数据的评估来确定。合适的营养培养基和/或替代品的选择应基于培养基和/或替代品模拟经评估能在无菌工艺中对产品无菌性构成风险的产品物理特性的能力。如果工艺操作可能间接影响被引入的任何微生物污染的活性（例如无菌生产的半固体、粉末、固体物料、微球、脂质体以及

产品被冷却或加热或冻干的其他配方），应开发尽可能代表该操作的替代程序。如果在 APS 的某些部分使用缓冲液等替代物料，则替代物料不应抑制任何潜在污染物的生长。

9.33 The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:

APS 应尽可能模拟日常无菌生产工艺，并包括所有关键生产步骤，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 应评估从工艺所用物料的灭菌和净化后到容器密封之间进行的所有无菌操作。

ii. For non-filterable formulations, any additional aseptic steps should be assessed.

对于不可过滤的制剂，应评估所有额外的无菌步骤。

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.

当在惰性气氛下进行无菌生产时，除非有意模拟厌氧条件，否则应在工艺模拟中用空气代替惰性气体。

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.

对于需要添加无菌粉末的工艺，应使用可接受的替代物料，置于被评估工艺所用相同容器中。

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.

应避免单个单元操作的分开模拟（例如，涉及干燥、混合、整粒和无菌粉末细分的工艺）。如要进行单独模拟，应有书面依据支持，并确保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.

冻干产品的工艺模拟程序应代表整个无菌工艺链，包括在规定的、有文件记录且经过论证的条件（代表最差条件下的操作参数）下的灌装、转移、装载、冻干室停留的代表性持续时间、卸载和密封。

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工艺的所有方面，除了那些可能影响污染物的活力或回收的方面。例如，应避免溶液沸溢或彻底冻结。在确定 APS 设计时要考虑的因素包括：

• The use of air to break vacuum instead of nitrogen or other process gases.

使用空气代替氮气或其它工艺气体来破真空。

• Replicating the maximum interval between sterilisation of the lyophilizer and its use.

重复冻干机灭菌与其使用之间的最长时间间隔。

• Replicating the maximum period of time between filtration and lyophilization.

重复过滤和冻干之间的最长时间。

• 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.

最差条件的定量方面，例如：装载托盘的最大载量，重复装载（冻干室与环境连通）的最长时间。

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 应考虑在正常生产以及最差条件下已知的各种无菌操作和干预措施，并考虑以下内容：

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.

应以与常规无菌工艺类似的方式和频率进行代表常规工艺的固有性和纠正性干预措施。

ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility.

应基于经评估的对产品无菌性的风险决定 APS 中的干预措施和频率。

9.35APS should not be used to justify practices that pose unnecessary contamination risks.

不应将 APS 用于证明造成不必要污染风险的行为的合理性。

9.36 In developing the APS plan, consideration should be given to the following:

在制定 APS 计划时，应考虑：

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.

确定涵盖相关变量的最差条件，例如容器尺寸和生产线速度以及它们对工艺的影响。评估的结果应证明选择的变量是合理的。

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。对于工艺等效性经科学论证的不同产品，如果使用相同的容器/密封件，可考虑采用括号法或矩阵法进行验证。

iii. Maximum permitted holding times for sterile product and equipment exposed during the aseptic process.

无菌工艺中暴露的无菌产品和设备的最大允许保留时间。

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足够，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组分表面。使用的体积应能提供足够的顶空，以支持潜在微生物生长，并确保在检查期间可以检测浊度。

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).

除非有意模拟厌氧，否则需要用空气代替日常无菌生产工艺所用的任何惰性气体。在这些情况下，应考虑将偶尔的厌氧模拟作为整体验证策略的一部分（参见第 9.33 节 iii 项）。

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.

所选的营养培养基应能够支持相关药典中的指定参照微生物以及具适当代表性的本地菌株的生长。

vii. The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.

检测微生物污染的方法应经过科学论证，确保能够可靠检出污染。

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.

工艺模拟应持续足够的时间以挑战工艺、执行干预的操作人员、换班以及工艺环境为无菌产品的生产提供适当条件的能力。

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.

如果有不同的班次或延长班次，那么 APS 应经过设计以获取经评估会对产品无菌性造成风险的那些班次的具体因素，例如操作人员在洁净室中的最长停留时间。

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中断（例如，换班、配药容器填料、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.

确保环境监测是按照常规生产的要求进行，并在整个工艺模拟持续期间一直监测。

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.

如果阶段式生产，例如使用屏障技术或生产无菌原料药，应考虑设计并执行工艺模拟以模拟与阶段开始和结束相关的风险，并证明阶段持续时间没有任何风险。

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.

“生产或阶段结束时的 APS”的表现可作为额外保证或用于调查；但如果使用，应在 CCS 中论证合理性，并且不应取代常规 APS。如果使用，应证明任何残留产品不会对任何潜在微生物污染的回收产生负面影响。

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 microorganisms.

对于无菌原料药，批量应足够大，以代表日常操作、模拟最差条件下的干预操作，并覆盖可能与无菌产品接触的所有表面。此外，所有模拟物料（替代品或生长培养基）应进行微生物评估。模拟物料应足以满足被模拟工艺的评估，并且不应有损微生物的回收。

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 应作为初始验证的一部分进行，至少有三个连续成功的、涵盖可能进行无菌工艺的所有工作班次的模拟试验，并且 APS 应在经评估对产品的无菌保证有影响的操作规范、设施、服务或设备的任何重大变更后进行（例如，HVAC 系统调整、设备变更、工艺变更、班次数量和人员数量变化、主要设施关停）。通常，对于每个无菌工艺，每个灌装线和每个班次，APS（定期再验证）应每年重复两次（大约每六个月一次）。每个操作人员应每年参与至少一次成功的 APS。应考虑在停产前最后一批之后、长时间闲置之前，或生产线停产或重新安置之前进行 APS。

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.

当发生手动操作（例如无菌配药或灌装）时，每种类型的容器、容器密封件和设备组应进行初始验证，每个操作人员至少参与 3 次连续成功的 APS，并且每个操作人员大约每 6 个月一次 APS 以进行再验证。APS 批量应模拟常规无菌生产工艺中使用的批量。

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.

APS 的加工（灌装）单元数应足以有效模拟代表无菌生产工艺的所有活动。应在 CCS 中明确记录待灌装单元数的合理性。通常，至少灌装 5000 至 10000 单元。对于小批量（例如 5000 单元以下），APS 的容器数量应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 nondestructive 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.

已灌装的 APS 单元在培养前应进行搅拌、旋转或倒置，以保证培养基与容器中的所有内表面接触。应培养和评估 APS 中的所有完整单元，包括具外观缺陷的单元或经非破坏性中控检查的单元。在工艺模拟过程中被剔除且未进行培养的单元数应与日常灌装中被剔除的单元数相当（仅在生产 SOP 明确规定相同条件下（即干预类型、生产线位置、剔除单元的具体数量）必须剔除单元时使用）。在任何情况下，培养基模拟灌装干预期间剔除的单元数都不应多于生产运行期间剔除的单元数，例如在日常生产中的组装过程后或特定类型的干预之后必须剔除的单元。为了充分了解工艺并评估无菌组装或强制性生产线清场期间的污染风险，这些单元通常会单独培养，并且不一定包括在 APS 的接受标准中。

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.

当工艺中包括与产品接触表面接触但随后被丢弃的物料时（例如产品冲洗），应用营养培养基模拟被弃物料并进行培养，作为 APS 的一部分，除非可以清楚地证明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.

已灌装的 APS 单元应在透明的容器中培养，以确保目测微生物生长。如果产品容器不透明（例如褐色玻璃、不透明塑料），可用相同构造的透明容器替代以帮助检测污染。当不能用相同构造的透明容器替代时，应开发并验证合适的微生物生长检测方法。从被污染单元中分离的微生物应在可行的情况下鉴定至种，以帮助确定污染物的可能来源。

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.

培养已灌装 APS 单元不应有非必须的延迟，以尽可能回收潜在微生物。培养条件和培养时长的选择应经过科学论证，并进行验证以提供适当水平的微生物污染检测灵敏度。

9.45 On completion of incubation:

培养完成后：

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.

已灌装的 APS 单元应由接受过适当的微生物污染检测培训和资质确认的人员进行检查。检查应在便于识别任何微生物污染的条件下进行。

ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.

已灌装单元的样品应设置阳性对照，即接种适当范围的参照微生物和具有适当代表性的本地菌株。

9.46 The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken:

目标应为无微生物生长。任何被污染的单元应致使 APS 失败，并应采取以下措施：

i. An investigation to determine the most probable root cause(s).

进行调查，确定最可能的根本原因。

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.

应进行足够数量的连续成功的重复 APS（通常至少 3 次）以证明工艺已恢复到受控状态。

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

及时回顾自上次成功 APS 以来所有与无菌生产有关的适用记录。

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 APS 以来生产的批次中潜在无菌偏差的风险评估。

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.

所有尚未放行至市场的其它批次应被纳入调查范围内。任何有关其放行状态的决定均应考虑调查结果。

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.

工艺模拟失败之后在生产线上生产的所有产品应被隔离待验，直到成功解决工艺模拟失败。

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.

如果根本原因调查表明失败与操作人员活动有关，则应采取措施以限制该操作人员的活动，直到其完成再培训和再次资质确认。

vii. Production should resume only after completion of successful revalidation.

只有成功完整再验证后才能恢复生产。

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.

9.47 所有 APS 运行应完整记录，并包括已处理单元的衡算（例如已灌装、已培养和未培养的单元）。已灌装和未培养的单元的论证应包含在文件中。应记录在 APS 过程中进行的所有干预操作，包括每次干预的开始和结束时间以及涉及的人员。所有微生物监测数据以及其它检测数据应记录在 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.

仅在书面规程要求商业化批次同等处理的情况下，才应中止 APS 运行。在这种情况下应记录调查。

9.49 An aseptic process should be subject to a repeat of the initial validation when:

在下列情况下，无菌工艺应重复进行初始验证：

i. The specific aseptic process has not been in operation for an extended period of time.

特定的无菌工艺长时间没有运行。

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 containerclosure combinations.

工艺、设备、程序或环境的可能会影响无菌工艺的变更，或增加新的产品容器或容器密封组合。

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.

应有接受过微生物学、无菌保证和工艺知识的适当培训并富有经验的人员，以支持生产活动的设计、环境监测管理以及评估微生物相关事件对无菌产品安全性的影响的任何调查。

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 表明需要控制微生物、微粒和内毒素/热原时，原辅料、零部件和产品的质量标准应包括微生物、微粒和内毒素/热原限度的要求。

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.

无菌灌装产品和最终灭菌产品的每个批次都应进行生物负载测定，并将结果作为最终批次审核的一部分。最终除菌级过滤器或最终灭菌工艺之前的生物负载应当有规定的限度，这与所用方法的效能有关。所取样品应代表最差条件（例如在保持时间结束时）。如果设定了最终灭菌产品过度杀灭法的灭菌参数，则应按照适当的时间间隔监测生物负载。

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.

对于批准参数放行的产品，应在启动灭菌周期之前为灌装产品制定预灭菌生物负载监测的支持性计划，并对每批产品进行生物负载分析。灭菌前灌装单元的取样位置应基于最坏情况，并能代表该批次。生物负载检测中发现的任何微生物都应进行鉴定，并确定其对灭菌工艺有效性的影响。必要时应监测内毒素/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.

成品的无菌检验应仅被视为确保无菌性的一系列关键控制措施中的最后一步。成品无菌检验不能用于确保不符合设计、程序或验证参数的产品的无菌性。成品无菌检验应用相关产品进行验证。

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:

无菌检验应在无菌条件下进行。用于无菌检验的取样应代表整个批次，但应特别包括该批次中被认为最具污染风险的部分样品，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。额外的样品应根据风险进行考虑，例如在关键干预之后取样。

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).

对于在最终容器内经过加热灭菌的产品，取样应代表最差条件下的位置（例如每批负载中可能最冷或最慢加热的部分）。

iii. For products which have been lyophilized, samples taken from different lyophilization loads.

对于已冻干的产品，从不同的冻干负载取样。

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：如果产生子批（例如最终灭菌产品），则应从每个子批中取样，并对每个子批进行无菌检验。对于其它成品检验，还应考虑单独检验。

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，可能无法在放行前获得无菌检验结果，因为产品的货架期太短而来不及完成无菌检验。在这些情况下，应评估并记录工艺设计的额外考虑以及缓解已识别风险所需的额外监测和/或替代检验方法。

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.

任何用于在检测之前对无菌样品的外表面进行净化处理的工艺（例如汽化过氧化氢、紫外）不应对无菌检验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检验。用于环境监测和 APS 的培养基在使用前应进行促生 K 试验，使用经过科学论证的指定参照微生物，并包括具适当代表性的本地菌株。培养基质量控制检验通常应由最终使用者进行。任何培养基委托检验或供应商检验都应经过论证，并且在这种情况下，应彻底考虑运输和发运条件。

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.

分级区域的环境监测数据和趋势分析数据应作为产品批次认证/放行的一部分进行审核。应提供一份书面规程，描述当发现环境监测数据超趋势或超出既定限度时应采取的措施。对于货架期较短的产品，可能无法获得生产时的环境数据;在这些情况下，合规应包括对最新可用数据的审核。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.

如果将快速和自动化微生物方法用于一般生产，这些方法应针对相关的产品或工艺进行验证。

Glossary

术语表

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：带互锁门的封闭空间,其构建目的是维持相邻房间（通常具有不同的空气洁净标准）之间的气压控制。气锁的目的是预防从较少控制区域微粒和微生物污染的侵入。

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：一种既定的相关指标（例如微生物限度或浮游微粒限度），当超过此限度时，应触发适当的调查和基于此调查的纠正措施。

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：一种既定的相关指标（例如，微生物或浮游微粒水平），给出正常操作条件和已验证状态的潜在漂移的早期警示，不一定成为纠正措施的依据，但会触发适当审查和跟进以解决潜在问题。警戒限是根据常规和确认的趋势分析数据建立，并定期回顾。警戒限可以基于许多参数，包括不良趋势、超出设定限度的个别偏移和重复事件。

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.

无菌制备/加工：在受控环境下对无菌产品、容器和/或器械的处理，受控环境是指送风、物料和人员受到管控以防止微生物、内毒素/热原和微粒污染。

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，以确认工艺确保产品无菌性的能力。包括与日常生产相关的所有无菌操作，例如必要的设备装配、制剂、灌装、冻干和密封工艺。

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并以防止微生物污染暴露的无菌产品的方式进行活动，从而获得的控制状态。

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 107 Colony Forming Units/cm^2.

细菌截留试验：进行该试验是为了验证过滤器可以去除气体或液体中的细菌。该试验通常采用标准微生物进行，例如最低浓度 10^7 菌落形成单位/cm^2 的缺陷短波单孢菌（Brevundimonas diminuta）。

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：一种通过将无菌工艺区（通常 A 级）与周围环境隔开，为无菌工艺区提供防护的物理隔断。此类系统经常部分或整体使用屏障技术，如 RABS 或隔离器。

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：与特定物相关的微生物总数，如人员、生产环境（空气和表面）、设备、产品包装、原材料（包括水）、中间体或成品。

Bio-decontamination - A process that eliminates viable bioburden via use of sporicidal chemical agents.

生物净化：通过使用杀孢子化学试剂消除活性生物负载的工艺。

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）：接种到适当培养基上（如溶液、容器或密封件）并放置在灭菌器或负载或房间的某位置来确定物理或化学处理的灭菌或消毒循环效能的一群微生物。挑战微生物的选择是根据其对给定工艺条件的抵抗性，并应进行验证。新批次的 D 值、微生物计数和纯度决定了 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（BFS）：一种由热塑性颗粒形成容器、灌装产品、然后密封的连续、集成、全自动操作技术。两种最常见的 BFS 机器类型是往复式（带有型坯切割）和旋转式（密封型坯）。

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.

阶段性生产：在给定的时间内，严格按照既定且经验证的控制措施对同一产品的一系列批次按顺序进行生产。

Classified area - An area that contains a number of cleanrooms (see cleanroom definition).

分级区域：包含许多洁净室的区域（见洁净室定义）。

Cleaning - A process for removing contamination e.g. product residues or disinfectant residues.

清洁：去除污染（如产品残留或消毒剂残留）的工艺。

Clean area - An area with defined particle and microbiological cleanliness standards usually containing a number of joined cleanrooms.

洁净区（：一种有明确的微粒和微生物洁净度标准的区域，通常包含数个相连的洁净室。

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：一种经设计、维护和控制以防止微粒和微生物污染药品的房间。这样的房间是指定的，可重复地符合适当的空气洁净水平。

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：一种根据洁净室或洁净空气设备的标准通过测定总微粒浓度来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：一种评估洁净室或洁净空气设备与其预期用途的符合程度的方法。

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：产品未暴露于周围环境的系统。例如，可以使用经由管道或管子彼此连接作为一个系统的散装产品容器（例如罐或袋）来实现，并且如果用于无菌产品，则在连接完成后对整个系统进行灭菌。密闭系统的例子可以是（但不限于）大规模可重复使用系统，例如原料药生产中所见到的系统，或一次性软袋和歧管系统，例如生物制品生产中所见到的系统。密闭系统在操作结束前不会被打开。本附录中使用的术语“密闭系统”并非指 RABS 或隔离器等系统。

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）：种微生物学术语，描述起源丁个或多个微生物的单个肉眼可见的菌落。对于液体样品，菌落形成单位通常表示为 CFU/ml,对于空气样品为 CFU/m^3，对于在固体培养基（例如沉降碟或接触碟）上的样品为 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：在生产、取样、包装或再包装、储存或运输过程中不期望地将微生物性质的杂质(微生物、热原的数量和类型)或外源微粒物引入原材料、中间体、原料药或药品中，可能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）：针对微生物、内毒素/热原和微粒的一系列有计划的控制措施，源于现有产品和工艺的理解并确保工艺性能和产品质量。控制措施可包括，原料药和制剂的物料和组分相关的参数和属性，厂房设施设备的操作条件，中间过程控制，成品质量标准，以及相关方法和监控频次。

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工艺的干预措施。在常规无菌工艺中可能不会以固定的频率发生。例如清除成分堵塞、堵塞泄漏、调整传感器和更换设备部件。

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：可能直接接触或直接影响无菌产品或其容器或密封件的表面。在生产操作开始前使关键表面灭菌，并在整个工艺中保持无菌。

Critical zone - A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.

关键区：位于无菌工艺区内的、产品和关键表面暴露于其中的位置。

Critical intervention - An intervention (corrective or inherent) into the critical zone.

关键干预：对关键区的干预（纠正性或固有性干预）。

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：将活性微生物数量减少至原始数量的 10%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 个内管直径的非循环管（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.

停产：工艺、设备或洁净室关闭并且将不再使用。

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.

净化：消除或减少区域、物体或人体的任何污染物（化学物质，废物，残留物或微生物）的整个过程。所用净化方法（例如清洁，消毒，灭菌）应进行选择和验证，以达到适用于被净化物品预期用途的洁净水平。另请参见生物净化。

Depyrogenation - A process designed to remove or inactivate pyrogenic material (e.g. endotoxin) to a specified minimum quantity.

除热原：旨在将致热物质（例如内毒素）去除或灭活至规定最小量的过程。

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：通过产品结构或代谢的不可逆作用，将微生物数量减少至被认为适合某特定用途的水平的过程。

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（：革兰氏阴性细菌细胞壁中存在的致热产物（即脂多糖）。内毒素能导致接受注射的患者发热至死亡的反应。

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：从参考测量点达到灭菌温度到负载内所有点达到灭菌温度之间的时间。

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：当在极端条件下暴露于适当溶剂中时从工艺设备表面迁移至被加工的产品或物料中的化学实体。

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.

首过气流：指在接触暴露的产品和产品接触表面之前没有被阻碍从而在到达关键区之前不太可能被污染的经过过滤的空气。

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：一种用以确认过滤器（产品，气体或 HVAC 过滤器）保持其截留特性并且在处理、安装或加工过程中没有被损坏的测试。

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。将连续的成卷的包装膜制成内包装容器，并同时对成型的容器进行产品灌装，然后对灌装好的容器进行密封，是一个连续的工艺过程。FFS 工艺可以利用单网系统（单个成卷的薄膜自身缠绕形成腔体）或双网系统（两个成卷的薄膜一起形成腔体），通常借助真空模具或加压气体。成型的腔体进行灌装、密封并切割成部分。薄膜通常由聚合材料、聚合涂层箔或其它合适的材料组成。

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：以初始和定期的方式确定个人穿戴完整工作服的能力的一个项目。

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：在没有要求进行总微粒连续监测、没有要求符合 A 级活性粒子监测限度的情况下，通过过滤器（经确认能够产生质量达到 A 级总微粒要求的空气）的空气。专门用于保护尚未轧盖的已完全加塞的西林瓶。

HEPA filter - High efficiency particulate air filter specified in accordance with a relevant international standard.

HEPA 过滤器：符合相关国际标准的高效空气过滤器。

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.

固有性干预：无菌工艺不可或缺的、在组装、常规操作和/或监测（例如无菌装配、容器补充、环境采样）中必须要进行的干预措施。关于无菌工艺执行的规程或工作指令要求固有干预。

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：一种降低连接过程中污染风险的装置；可以由机械密封或熔融密封。

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).

等速采样头：一种旨在尽可能少地扰乱空气、使进入管口的微粒与管口不存在时通过该区域的微粒相同的采样头（即能够使进入样品探针入口处的空气流速与该位置气流的平均流速几乎相同（±20%）的采样条件)。

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，内部工作区符合 A 级条件，提供其内部环境与外部环境（例如周围洁净室空气和人员）的不受损害的、连续的隔离。有两种主要类型的隔离器：

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.

密闭隔离器系统通过与辅助设备的无菌连接而不是对周围环境开放来完成物料转移，从而阻断外部污染物进入隔离器内部。密闭系统在整个操作中保持密封。

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.

开放隔离器系统的设计允许操作过程中物料通过一个或多个开口连续或半连续进出。开口从工程学上（如使用连续过压）阻断外部污染进入隔离器。

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.

可浸出物：在正常使用和/或储存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实体。

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.

本地菌株：经常性从分级区的环境监测（特别是 A 级和 B 级区）、人员监测或阳性无菌检验结果中回收到的、能适当地代表场地微生物的微生物菌株。

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：一种通过升华方式去除水性和非水性体系中溶剂的物理化学干燥工艺，主要是为了达到产品或物料的稳定性。冻干是术语冷冻干燥（freeze-drying）的同义词。

Manual aseptic processing— An aseptic process where the operator manually compounds, fills, places and /or seals an open container with sterile product.

手动无菌工艺：操作人员手动配药、灌装、放置和/或密封无菌产品敞口容器的无菌工艺。

Operator - Any individual participating in the processing operation, including line set-up, filling, maintenance, or other personnel associated with manufacturing activities.

操作人员：任何参与工艺操作（包括线组装、灌装、维护）的个人，或与生产活动有关的其他个人。

Overkill sterilisation - A process that is sufficient to provide at least a 12 $\log_{10}$ reduction of microorganisms having a minimum D-value of 1 minute.

过度杀灭灭菌：一种足以将最小 D 值为 1 分钟的微生物降低 12 个对数值的工艺。

Parison - The "tube" of polymer extruded by the BFS machine from which containers are formed.

型坯：由 BFS 机器挤出的聚合物的“管”，用于形成容器。

Pass-through hatch - Synonymous with airlock (see airlock definition) but typically smaller in size.

传递窗：与气锁同义（参见气锁定义），但通常较小。

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, Fo>8 min) are not fulfilled. This may also be beneficial in the destruction of viruses that may not be removed through filtration.

无菌工艺后最终热处理：无菌工艺后采用的最终湿热工艺，已被证明可提供无菌保证水平（SAL）$<10^{-6}$ 但不满足蒸汽灭菌的要求（例如 F_0>8 分钟）。这也可能有利于破坏可能无法过滤去除的病毒。

Pyrogen - A substance that induces a febrile reaction in patients receiving injections;

热原：—种引起接受注射的患者发热反应的物质；

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.

快速转移系统/接口（RTP）：一种用于将物品转移到 RABS 或隔离器中的系统，最大程度降低对关键区的风险。一个例子是具有 a/8 接口的快速转移容器。

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：拟用于无菌产品生产的任何成分，包括成品中可能没有的成分。

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.

限制进入隔离系统（RABS）：提供一个封闭但未完全密封、符合规定的空气质量条件的环境（对于无菌工艺为 A 级）并使用刚性外壳和一体式手套使内部与周围洁净室环境隔开的系统。RABS 的内表面用杀孢子剂进行消毒和净化。操作人员使用手套、半身工作服、RTP 和其它集成转移接口操纵或传输物料至 RABS 内部。根据设计，RABS 的门很少会开启，并且仅在严格的预先定义的条件下打开。

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.

一次性系统（SUS）：产品接触组分仅使用一次的系统，代替可重复使用的设备，例如不锈钢输送线或散装容器。本文件中的 SUS 是指那些用于无菌产品生产的 SUS，通常由一次性组分组成，例如袋子、过滤器、管子、接头、储瓶和传感器。

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：一种以足够浓度使用时在特定接触时间内会破坏细菌和真菌孢子的试剂。预期会杀死所有的有生长力的微生物。

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：本指南中，无菌产品指的一种或多种经灭菌、暴露于无菌条件下并最终制成无菌原料药或无菌成品制剂的组分。这些组分包括容器、密封件和成品制剂的成分。或者，是指通过最终灭菌工艺灭菌的产品。

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 0.22µm.

除菌级过滤器：一种经过适当验证、去除液体或气体中的特定微生物以产生无菌滤液的过滤器。通常这种过滤器的孔径等于或小于 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 1×10^{-6} (one in a million)).

最终灭菌：对最终容器内的产品施用有效的灭菌剂或灭菌条件，以达到预定的 10^{-6} 无菌保证水平（SAL）或更好（例如已灭菌单元表面或内部存在单个活微生物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：非单向流动的空气。洁净室中的湍流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：以单一方向、稳定和均匀方式、以及足够速度移动的气流，可重复地将微粒从关键操作区或检测区扫除的气流。

Unidirectional Airflow (UDAF) unit - A cabinet supplied with filtered unidirectional airflow (previously referred to as a Laminar Airflow Unit or LAF).

单向流（UDAF）单元：提供经过滤的单向流的机柜（之前称为层流单元或层 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：包含加工限度和情况的一组条件，包括标准操作规范内的、有最大可能导致工艺或产品失败的条件(与理想条件相比)。这样的条件有最大可能、但不一定总是导致产品或工艺失败。

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：水的生产、储存和分配系统，通常符合药典的特定级别（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 倍的温度差。