Points to Consider No. 1:
Aseptic Processing (Revised 2023)

考虑要点 No.1：
无菌加工（2023 年修订版）

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Introduction 简介

Points to Consider No. 1: Aseptic Processing (Revised 2023) offers PDA's thoughts and does not represent a standard or regulatory guidance.
*考虑要点 1：无菌加工（2023 年修订版）*提供了 PDA 的想法，但并不代表标准或监管指南。

PDA first issued *Points to Consider for Aseptic Processing* in 2003. To address the impact of the knowledge gained in the intervening years, PDA assembled a task force of subject-matter experts from industry to revise this report. Published in 2015 and 2016, *Points to Consider for Aseptic Processing* parts 1 and 2 provided positions on current topics, best practices, and areas of clarification important to the manufacture of quality sterile products.
PDA 于 2003 年首次发布了《*无菌加工考虑要点*》。为了应对这些年所获得相关知识的影响，PDA 组建了一个由来自行业的主题专家组成的工作组来修订该报告。《*无菌加工考虑要点*》第 1 部分和第 2 部分于 2015 年和 2016 年出版，它提供了关于当前话题、最佳实践以及对生产高质量无菌产品至关重要的澄清领域的观点和建议。

NOTE: The topics discussed in the 2015 and 2016 Points to Consider documents are superseded by this revision.
注：2015 年和 2016 年 "考虑要点 "文件中讨论的主题已被本修订版取代。

With technology and regulatory advancements, specifically the issuance of the revised *European GMP Annex 1: Manufacture of Sterile Medicinal Products (EU Annex 1*[1]*)* in August 2022, another update of this document was undertaken. This revision reflects current industry best practices and scientific positions as well as regulatory expectations. Where there may be a divergence between recommendations in this Points to Consider document and a regulatory position, that divergence is noted.
随着技术和监管的进步，特别是 2022 年 8 月发布的修订版《*欧洲药品管理局附录 1：无菌药品生产》(EU Annex 1)*，本文件进行了另一次更新。此次修订反映了当前行业最佳实践、科学立场以及监管预期。如果在本《考虑要点》文件和监管立场之间存在分歧，该分歧将会进行记录。

Many of the topics included in the 2015 Points to Consider resulted from discussion and input from PDA members at conferences and meetings. These topics were reviewed considering the advancements made in the past decade and, where applicable, this report has been revised based on similar inputs.
2015 年《考虑要点》中包含的许多主题来自 PDA 成员在各种会议上的讨论和意见。考虑到过去十年取得的进步，我们对这些主题进行了审核，并在适用的情况下，根据类似意见对本报告进行了修订。

While the current revision maintains the original organization of topics into categories, topics that had been discussed separately in Parts 1 and 2 have been combined into a single document. Each topic discussion begins with a problem statement in the form of a question about issues or points needing clarification on that specific topic. Recommendations from the PDA task force are then presented as an answer to the question. The rationale and references for each recommendation follow.
本次修订保留了原来的专题分类组织结构，但将第 1 部分和第 2 部分分别讨论的专题合并为一份文件。

[1] The PIC/S GMP Annex 1 is identical to the EU Annex 1 and, hereafter, EU Annex 1 means EU-PIC/S Annex1.
PIC/S GMP 附录 1 与欧盟附录 1 相同，以下欧盟附录 1 指欧盟-PIC/S 附录 1。

每个话题的讨论都以关于该特定话题需要澄清的问题形式的问题陈述开始。然后，PDA 工作组的相关建议以回答这个问题的方式呈现出来。每个建议的理由和参考文献随后附在后面。

This document provides points to consider on topics related to the physical environment in which aseptic processing is conducted, monitoring of that environment, cleanroom personnel, material transfer, aseptic-process simulation and validation, “modern” blow-fill-seal technology, cleaning, disinfection and sterilization, and critical utilities. It also includes points to consider on aspects of filter-integrity testing and water-for-injection (WFI) preparation. For additional information on specific topics, other PDA points to consider, technical reports, or similar documents are referenced. The recommendations presented in this Points to Consider document are based on five guiding and linked principles for improvement in sterile health care products:

本文件提供了关于无菌加工所进行的物理环境、该环境的监测、洁净室人员、物料转运、无菌工艺模拟和验证、"现代"吹灌封技术、清洁、消毒和灭菌以及关键设施等相关话题的考虑要点。它还包括有关过滤器完整性测试和注射用水（WFI）制备的考虑要点。对于特定话题的额外信息，会引用其他 PDA 的考虑要点、技术报告或类似文件。本《考虑要点》文件中提出的建议是基于改进无菌医疗保健产品的五项指导和相关原则：

1. Scientifically sound, risk-based approaches should be used to obtain information needed to make decisions related to the evaluation, design, qualification, operation, and monitoring of sterile-product manufacturing processes. Risk- and science-based approaches should be used as well to develop and implement control strategies and acceptance criteria designed to ensure the establishment and maintenance of manufacturing conditions that affect the sterility of products. Sterile drug-product manufacturing processes and testing requirements should have a basis in and relevance to risks to product quality and patient safety. Similar principles and considerations may also apply to non- sterile drug products. Risk management and assessment methods should be developed not only to identify risks, but also to allow the improvement of processes and control strategies.
   应使用科学合理的、基于风险的方法来获取制定与无菌产品制造过程的评估、设计、确认、运行和监测相关决策所需的信息。同时，还应采用风险和科学为基础的方法来制定和实施控制策略和验收标准，以确保建立和维护影响产品无菌性的制造条件。无菌药品制造过程和测试要求应该基于和与产品质量和患者安全风险有关。类似的原则和考虑也可能适用于非无菌药品。风险管理和评估方法不仅用于识别风险，还应允许改进过程和控制策略。

2. Where feasible, the use of newer technologies should be considered to mitigate or reduce risks to product quality identified in manufacturing processes and operations. Companies involved in the manufacture of sterile drug products should be encouraged to identify and consider the use of modern technologies, and regulatory guidance should enable this by presenting expectations that encourage the use of these technologies. Technologies and facility, equipment, and process designs that protect products and product-contact surfaces from personnel and environmental contact and that provide more reliable and useful information are particularly beneficial to reducing the risk of microbiological contamination during aseptic processing.
   在可行的情况下，应考虑使用新技术来减轻或降低在制造过程和运营中识别的产品质量风险。参与无菌药品制造的公司应被鼓励识别和考虑使用现代技术，而监管指南应鼓励使用这些技术，提出预期，以使其成为可能。那些能够保护产品和产品接触表面免受人员和环境接触，并提供更可靠和有用信息的技术以及设施、设备和工艺设计，对于降低在无菌加工过程中微生物污染风险特别有益。

3. The effectiveness of certain traditional testing and monitoring methods used as control strategies should be reevaluated. As technology has been introduced and knowledge has been acquired, the usefulness and value of testing procedures have changed. Testing and monitoring should be designed and performed, and the results should be evaluated, based on scientific value, risk to product quality, patient safety, and usefulness in determining process control. Where testing and monitoring approaches and methods no longer meet current needs or are not optimal, their replacement or modification should be considered. The use of outdated testing and monitoring methods has the potential to increase risk, provide a false sense of control, prove ineffective, and deploy resources in a manner that may not be efficient or optimal, thus detracting from the development and use of more effective testing and monitoring approaches.
应重新评估作为控制策略使用的某些传统测试和监测方法的有效性。随着技术的引入和知识的积累，测试程序的实用性和价值已经发生了变化。测试和监测应根据科学价值、对产品质量的风险、患者安全以及确定工艺控制的实用性来设计和执行，并应对结果进行评估。当测试和监测方法不再满足当前需求或不是最佳选择时，应考虑替代或修改。使用过时的测试和监测方法可能增加风险，提供虚假的控制感，证明无效，并以可能不是高效或最佳的方式部署资源，从而削弱了更有效的测试和监测方法的开发和使用。

4. New product/container presentations, therapies, and technologies present challenges to existing methods for the development, manufacture, validation, and testing of sterile products. To meet these challenges, an emphasis on thorough technical and process understanding, science, and risk will become important in designing effective means to ensure product quality. Companies should be encouraged to seek out the most effective means rather than try to fit traditional methods to these new products, technologies, and therapies.
新的产品/容器形式、疗法和技术对无菌产品的开发、制造、验证和测试现有方法提出了挑战。为了迎接这些挑战，在设计有效的手段以确保产品质量方面，强调充分的技术和过程理解、科学和风险将变得重要。公司应被鼓励寻求最有效的方法，而不是试图将传统方法应用于这些新产品、技术和疗法。

5. When scientific approaches are similar and agreed upon, global health authority requirements and guidance should be consistent in technical language and definition. Harmonized technical and regulatory language, where possible, should be consistent with approaches presented in other similar guidance documents. This practice should promote clarity of global regulatory expectations and reduce the risk of misunderstanding and redundant efforts.
当科学方法相似并得到一致认可时，全球卫生管理机构的要求和指导应在技术语言和定义上保持一致。在可能的情况下，协调的技术和监管语言应与其他类似指南文件中提出的方法保持一致。这一做法应该有助于明确全球监管的期望，减少误解和冗余工作的风险。

Glossary 术语表

Definitions have been provided to help clarify the concepts discussed in this document. While some of the definitions vary among companies, the definitions described below are consistent for use within this Points to Consider document. Where a definition is based on another published source, the source is cited.
提供定义以帮助澄清本文件中讨论的概念。虽然一些定义在公司之间可能存在差异，但下面描述的定义在本《考虑要点》文件中的使用是一致的。如果一个定义是基于其他已发布的来源，那么将引用出处。

Aborted Run
终止运行
Aseptic process simulation run that begins and is then stopped and not filled to completion.
无菌工艺模拟运行，开始后被停止并未完成灌装。

Action Limit
行动限
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 (1).
已建立的相关判断标准（例如，微生物或空气悬浮粒子的限制），当超出时，应触发适当的调查和根据调查采取的纠正措施（1）。

NOTE: In a prior version of this document, this term was called "Action Level."
注：在本文件的上一版本中，该术语被称作"行动水平"。

Advanced Aseptic Processing Personnel Qualification
高级无菌加工人员的资格确认
A defined and documented procedure for determining the criteria by which personnel are permitted to enter and perform higher-risk and complex activities, under less supervision, in the aseptic processing area during commercial operations. **(See Section IV, Topic B.)**
一项明确定义和文件化的程序，用于确定人员被允许在商业化生产操作期间在无菌加工区域进行高风险和复杂活动，而无需过多监督的标准。 **(参见第四部分，主题 B)**

Air Shroud
气流罩（空气幕）
A physical enclosure for a blow-fill-seal (BFS) machine that contains or surrounds the filling zone. It is typically supplied by sterile filtered or Grade A quality air. The air shroud should be sterilized or decontaminated to maintain Grade A conditions.
气流罩是用于包围吹-灌-封（BFS）设备的填充区域的物理封闭设备。通常，它通过经过无菌过滤或 A 级质量的空气供应。气流罩应进行灭菌或除污以维持 A 级条件。

Air Visualization Studies/Airflow Visualization Studies
空气可视化研究/气流可视化研究
Tests using a visible medium (e.g., smoke or vaporized liquid nitrogen) simulating the properties of air flow, designed to indicate the direction and disruption of air flow. Sometimes referred to as 'smoke studies'.

使用可见介质（例如：烟雾或液氮蒸发）进行的测试，模拟空气流动的特性，旨在指示空气流动的方向和扰动情况。有时也称为 "烟雾研究"。

Aseptic Preparation/Processing
无菌准备/加工
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 (1).
在受控环境中处理无菌产品、容器和/或设备，其中空气供应、材料和人员都受到监管，以防止微生物、内毒素/热源和颗粒污染。

Aseptic Process Simulation (APS)
无菌工艺模拟（APS）
A means for establishing the capability of an aseptic process as performed using a growth medium.
一种利用生长培养基确定无菌工艺能力的方法。

At-Rest
静态
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 with- out personnel present in the room (1).
指所有设施设备已经安装完成，包括正常运行的暖通空调净化系统（HVAC），主要的生产设备按照规定进行了安装，但尚未运行，房间内没有人员在场的状态。

Blow-Fill-Seal (BFS) Process
吹-灌-封（BFS）工艺
The BFS machine, including the parison extrusion, parison transport (if applicable), container filling and final sealing operations.
BFS 机器，包括坯料挤出、坯料传输（如适用）、容器灌装和最终密封操作。

NOTE: Some companies refer to this process as “Form-Fill-Seal” (FFS). However, EU Annex 1 defines Form-Fill-Seal as “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” (1).
注：有些公司将这种工艺称为“成型-灌-封（FFS）”。然而，欧盟附录 1 将成型-灌-封（FFS）定义为“一种自动化灌装过程，通常用于最终灭菌的产品，它是通过使用连续的平卷包装薄膜构建主要容器，同时将已成型的容器填充产品，并在一个连续的过程中密封已填充的容器”（1）。

Corrective and Preventive Actions (CAPA)
纠正和预防措施（CAPA）
Actions to eliminate the cause of a detected nonconformity or other undesirable situation.
消除已发现的不符合项或其他不良情况的原因的行动。

NOTE: Corrective actions are taken to prevent recurrence, whereas preventive actions are taken to prevent

occurrence.

注：纠正措施旨在防止再次发生，而预防措施旨在防止发生。

Cleaning Agents

清洁剂

The solution or solvent used in the washing step of a cleaning process. Examples of cleaning agents are water, organic solvent, commodity chemical diluted in water, and formulated detergent diluted in water.

清洁过程中用于清洗步骤的溶液或溶剂。清洁剂的示例包括水、有机溶剂、在水中稀释的商品化学品以及在水中稀释的配方洗涤剂。

Closed Parison (Rotary or Reciprocating Machines)

封闭坯料（旋转式或往复式机器）

BFS machines that use a fill system enclosed in the continuous parison. Containers are closed in such a way as to not expose the parison interior or fill zone to the environment.

BFS 机器采用连续坯料中的封闭灌装系统。容器以一种不会暴露坯料内部或灌装区域给环境的方式进行封闭。

Contamination Control Strategy (CCS)

污染控制策略（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 (1).

是指一套计划的控制措施，用于控制微生物、内毒素/热源和颗粒，这些措施是基于对当前产品和工艺的理解，并确保了工艺性能和产品质量。这些控制措施可以包括与活性物质、辅料和药品成分、设施和设备操作条件、工艺中的控制、成品规格以及相关的监测和控制方法和频率相关的参数和属性（1）。

Critical Surface

关键表面

A surface within a critical zone that may come in direct contact with sterilized products, containers, or closures.

关键区内的表面，可能直接接触到已灭菌的产品、容器或密封件。

Critical Zone

关键区

A location within the aseptic processing area in which product and critical surfaces are exposed to the environment (1).

在无菌加工区域内的位置，其中产品和关键表面暴露在环境中。

NOTE: This term was previously referred to as “Critical Area.”

注：该术语之前称为“关键区域”。

Disinfectant

消毒剂

A chemical or physical agent that reduces, destroys, or eliminates vegetative forms of harmful micro-organisms, but not spores.
一种化学或物理试剂，可以减少、破坏或消除有害微生物的有丝分裂形态，但不能杀灭孢子。

Disqualification of Aseptic Processing Personnel
无菌加工人员资格的取消
A defined and documented procedure for determining the criteria by which previously qualified aseptic processing personnel are no longer permitted to enter and perform higher-risk and complex activities in the aseptic processing area during commercial operations. (See Section IV, Topic B: Aseptic Personnel Qualification Program.)
一项明确定义和文件化的程序，用于确定以前获得资格的无菌加工人员不再被允许在商业化生产操作期间进入无菌加工区域并进行高风险和复杂活动的标准。（参见**第四部分，主题 B**：无菌人员资格认定计划。）

Environmental Monitoring (EM)
环境监测（EM）
Describes the processes and activities that need to take place to characterize and monitor the quality of the environment.
描述表征和监测环境质量所需的过程和活动

First Air
初始气流
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 (1).
指的是在接触暴露的产品和产品接触表面之前未受到干扰的经过滤的空气，这种干扰有可能在气流抵达关键区之前向空气中引入污染。

Grade A Air Supply
A 级送风
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 (1).
通过合格的过滤器传递的空气，该过滤器能够产生符合 A 级总粒子质量的空气，但无需进行连续的总粒子监测或满足 A 级活性颗粒监测限制的要求。主要用于保护完全压塞，但尚未被轧盖的西林瓶。

Good Manufacturing Practice (GMP)
药品生产质量管理规范（GMP）
Best practices in manufacturing of pharmaceuticals or biopharmaceuticals. From a regulatory stand- point, GMPs are regarded as the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packaging, or holding of a drug to assure that such drug meets the requirements of safety, identity, and strength and meets the quality and purity characteristics that it purports or is represented to possess.
制药或生物制药制造的最佳实践。从监管角度来看，GMP（**药品生产质量管理规范**）被视为制药工艺和设施或控制方法的最低标准，用于制造、加工、包装或储存药物，以确保这种药物满足安全性、识别性和强度要

求，并满足其所宣称或所表示的质量和纯度特征。

High-Efficiency Particulate Air (HEPA) Filter
高效粒子过滤器（HEPA）
High efficiency particulate air filter with minimum 0.3 µm particle retaining efficiency of 99.97 percent (3).
高效粒子空气过滤器，0.3µm 粒子过滤孔径，过滤效率最低达到 99.97%（3）。

In-Operations
动态
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 maxi- mum number of personnel present performing or simulating routine operational work (1).
指洁净室的安装已经完成，暖通空调系统已经完全运行，设备已经安装并按制造商定义的操作模式运行，同时有最多的人员在场，执行或模拟日常操作（1）。

Invalid Run
无效运行
Aseptic processing simulation run that was filled to completion and then invalidated.
指完成灌装后并作废的无菌工艺模拟运行。

Isolator
隔离器
A contained, decontaminated environment meeting Grade A/ISO 5 conditions used for aseptic process manufacturing that provides an uncompromised, continuous isolation of its interior from the external environment. Once decontaminated by a validated cycle, an isolator prevents the microbiological contamination of sterile products and product contact surfaces of the interior by enclosures and the supply of continuous, controlled overpressure of HEPA-filtered air. (2)
符合 A/ISO 5 级条件的用于无菌工艺制造的封闭、去污环境，其内部与外部环境实现无损、连续隔离。隔离器通过有效的循环进行净化后，通过封闭和持续提供受控的正压 HEPA 过滤空气，可防止内部无菌产品和产品接触面受到微生物污染。(2)

> **Closed isolator systems** exclude external contamination from the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than using openings to the surrounding environment. Closed systems remain sealed throughout operations (1).
> **密闭式隔离器系统**通过与辅助设备的无菌连接实现物料转移，而不是利用与周围环境的开口，从而将外部污染排除在隔离器内部之外。封闭式系统在整个操作过程中保持密封（1）。

> **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 contamination into the isolator. (1)
> **开放式隔离器系统**的设计允许物料在操作过程中通过一个或多个开口连续或半连续地进入和/或排出。开口的设计（如使用持续正压）可防止外部污染物进入隔离器。(1)

Initial Aseptic Processing Personnel Qualification

无菌加工人员初始资格确认

A defined and documented procedure for determining the criteria by which personnel are permit- ted to enter and perform certain low-risk and less complex activities, under direct supervision, in the aseptic processing area during commercial operations. (See **Section IV, Topic B**.)

在商业化生产操作过程中，确定允许人员进入无菌处理区并在直接监督下从事某些低风险和不太复杂活动的标准的规定程序，并形成文件。(见**第四部分，主题 B**)。

Ongoing Aseptic Processing Personnel Assessment

无菌加工人员的持续评估

A defined and documented procedure for determining the criteria by which the performance of personnel, deemed as qualified to enter and perform activities in the aseptic processing area during commercial operations, is assessed on a prescribed, periodic basis. (See **Section IV, Topic B**.)

明确规定并要求记录的程序，用于确定标准，据此在规定的基础上定期评估被视为有资格在商业运营期间进入无菌加工区并从事相关活动的人员的表现。(见**第四部分，主题 B**)。

Open Parison (Shuttle Machines)

开放式型坯（穿梭机）

Blow-fill-seal machines where the parison is cut from the extruder and the open parison is contained in the mold during transport to the critical fill zone.

吹-灌-封设备，型坯从挤出机切下，在输送到关键灌装区的过程中，开放式型坯被控制在模具中。

Requalification of Aseptic Processing Personnel following Disqualification

无菌加工人员被取消资格后的资格再确认

A defined and documented procedure for determining the criteria by which previously disqualified aseptic processing personnel are again permitted to enter and perform activities in the aseptic processing area during commercial operations. (See **Section IV, Topic B**.)

一个明确规定并要求记录的程序，用于确定先前被取消资格的无菌加工人员在商业化生产操作期间再次获准进入无菌加工区并从事相关活动的标准。(见**第四部分，主题 B**)。

Restricted Access Barrier System (RABS)

屏障隔离系统（RABS）

An area that includes one or more critical work areas that is fully or partially enclosed with ridged or semi-rigid walls, which restricts the access of aseptic processing personnel, via fixed gloves, to the critical work area during aseptic operations.

包括一个或多个关键工作区的区域，全部或部分用突出或半刚性墙封闭，让无菌操作人员在无菌操作期间通过固定于工作区上的手套接触关键工作区。

Sanitizers

消毒剂

A compound that will reduce the number of vegetative microorganisms to a safe level as determined by public health requirements. Normally, a reduction of 103 in vegetative microorganisms is obtained.

一种可将营养型微生物数量减少到公共卫生要求所确定的安全水平的化合物。通常情况下，可将营养型微生物的数量消除至千分之一。

Total Particulate

总粒子

Refers to what is often termed “nonviable particles,” which, in fact, are measures of both viable and nonviable particulates.

和通常所说的 "无存活性粒子"有关，实际上是全部有存活性粒子和无存活性粒子的量。

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I. Physical Environment 物理环境

Topic A.1: Airflow Velocity 主题 A.1：风速

Problem Statement
问题陈述

Where should airflow velocity measurements be taken with respect to a filling line or other aseptic processing areas?
应在灌装线或其他无菌生产区域的哪个位置测量风速？

Recommendation
建议

Airflow velocity measurements should be taken at locations where critical surfaces or products are exposed, and should be protected by "first air," that is, at working height or elsewhere that would yield valuable information (e.g., at a distance of 15-30 cm from filter face). Measurement location may need to be modified due to equipment configuration that results in interference of airflow velocity as identified by risk assessment and rationalized and documented by the contamination control strategy (CCS). Readings should be reproducible.
风速测量应该在暴露关键表面或产品的位置进行，并且应该受到"初始气流"的保护，即在工作高度或其他能提供有价值信息的地方（例如，距离过滤器面 15-30 厘米的距离）。由于设备配置导致风速干扰，测量位置可能需要进行调整，这应通过风险评估确定，并由污染控制策略（CCS）加以科学的说明和记录。测量结果应具有重现性。

Rationale
理由

The primary reason for airflow velocity measurements in unidirectional airflow areas (e.g., areas where products, product-contact packaging components, and product-contact surfaces are exposed) is to ensure adequate airflow to protect the materials from external airborne contamination and to verify continued compliance with current smoke studies. The adequacy of the environment can be determined, in part, from airflow velocity and airflow visualization studies, and from particulate matter monitoring (at the working position).
在单向气流区域（如产品、产品接触包装部件和产品接触表面暴露的区域）测量风速的主要目的是确保有足够的气流来保护物料免受外部空气污染，并验证是否继续符合当前的烟雾研究结果。环境是否适当在一定程度上可通过风速、气流可视化研究以及粒子监测（在工作位置）来确定。

Accurate measurements can be taken and changes over time can be detected when airflow velocities are evaluated at a predetermined distance from the filter surface that is sufficiently close to the filter surface to be reproducible to detect changes in the performance of the filter.
在距离过滤器表面足够近的预定距离处对风速进行评估时，可以进行精确测量并检测出随着时间的推移而发生的变化。

These data must be paired with an airflow visualization study to provide evidence of adequate protection of the aseptic process when the air velocity is in a specific range (and no change in the design of the area has occurred).

这些数据必须与气流可视化研究相结合，以证明当风速在特定范围内时（且该区域的设计未发生变化）无菌工艺得到了充分保护。

The airflow velocity depends on the design of the filling line, room design, and air-handling system. (See also Section I, Topic A.2: Air Flow Velocity Measurements.) Once velocity is determined, it is important to ensure that the velocity stays within the specified parameters. Routine air velocity measurements should be taken at the same locations used during the initial airflow studies to ensure consistency.
风速取决于灌装线的设计、房间设计和空气处理系统。(另请参见第 I 部分，主题 A.2：风速测量)。一旦确定了速度，就必须确保速度保持在规定的参数范围内。应在初始气流研究时使用的相同位置进行常规风速测量，以确保一致性。

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Topic A.2: Airflow Velocity Measurements 主题 A.2：风速测量

Problem Statement
问题陈述
Is an airflow velocity of 0.45 meters/sec ± 20% a requirement at the working surface in a critical zone?
关键区工作表面的风速是否需要达到 0.45 m/s ± 20%?

Recommendation
建议
Airflow patterns should be sufficient to protect exposed products, product-contact packaging components, and product-contact surfaces from the ingress of potential environmental contaminants outside the critical zone. Unidirectional flow is an important factor in providing this protection. Although a linear air velocity of 0.45 meters/sec ± 20% when measured 15 cm to 30 cm from the filter face is a commonly recommended range to establish unidirectional airflow, this should not be considered a requirement at the working level. The velocity ranges at the working level and at the filter face should be established and justified in the CCS. Performing this test in conjunction with air visualization studies can also demonstrate the maintenance of unidirectionality at the working height, and this should be done at both at-rest and in-operation situations.
气流模型应足以保护暴露在外的产品、与产品接触的包装部件以及与产品接触的表面，使其免受关键区域外潜在环境污染物的侵入。单向气流是提供这种保护的一个重要因素。虽然在距离过滤器表面 15 cm 至 30 cm 处测量 0.45 m/s ± 20% 的线性风速是建立单向气流的常用推荐范围，但这不应被视为工作层的要求。工作层和过滤器面的速度范围应在 CCS 中确定并说明理由。结合空气可视化研究进行该测试还可证明在工作高度保持单向性，该测试应分别在静态和动态下进行。

Rationale
理由
Airflow velocity and pattern are dependent upon obstacles encountered within the critical zone, including the filling equipment/line, interventions by personnel, and configuration of the barrier that separates the zone from the outer environment. Unidirectional flow is intended to allow the air to flow smoothly past and around these obstacles with minimal turbulence and no induction of potential contamination from outside the zone. The supply air velocity should be correlated to airflow visualization studies and optimized to produce airflow patterns that protect exposed products, product-contact packaging components, and product-contact surfaces from airborne contamination at the working level. This may be lower (or even higher) than the recommended accepted range.
风速和流型取决于关键区内遇到的障碍，包括灌装设备/生产线、人员干预以及将关键区与外部环境隔开的屏障的配置。单向流动的目的是让空气平稳地流过和绕过这些障碍物，同时将湍流降至最低，并避免从区域外引入潜在污染。送风速度应与气流可视化研究相关联，并进行优化，以产生保护暴露产品、产品接触包装部件和产品接触表面免受工作层空气污染的气流模型。这可能低于（甚至高于）建议的接受范围。

NOTE: Current EU Annex 1 (2022) states “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.” The air velocity range is specifically indicated as a guidance.
注： 目前的欧盟附件 1（2022 年）规定："单向气流系统应在工作位置提供 0.36 - 0.54 m/s（指导值）范

围内的均匀风速，除非 CCS 另有科学依据。气流可视化研究应与气速测量结果相关联"。风速范围被明确指出为指导值。

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Topic A.3: Airflow Velocity Measurement Frequency

主题 A.3：风速测量频率

Problem Statement
问题陈述
When do airflow velocity measurements have to be taken?
何时须测量风速?

Recommendation
建议
Airflow velocity measurements should be taken during operational and performance qualification studies. High-efficiency particulate air (HEPA) filters in critical zones (i.e., Grade A and surrounding Grade B areas) should then be tested every six months, and the frequency of testing HEPA filters in other areas should be at least annually. More frequent measurements may be appropriate if other measures of cleanroom quality indicate a significant deviation (e.g., increased airborne particulates). The impact of air velocity levels that are outside validated acceptance criteria should be evaluated by performing airflow visualization studies as part of applicable change-management procedures.
应在运行和性能确认研究期间测量风速。关键区域（即 A 级和背景 B 级区域）的高效空气过滤器应每六个月检测一次，其他区域的高效空气过滤器至少应每年检测一次。如果洁净室的其他质量指标显示存在显著偏差（如空气中的微粒增多），则应更频繁地进行测量。应通过气流可视化研究来评估超出验证验收标准的风速水平的影响，并将评估结果作为适用的变更管理程序的一部分。

Rationale for Recommendation
建议的理由
Airflow velocity is measured to ensure adequate airflow to protect exposed products, product-contact packaging components, and product-contact surfaces. It is also measured to ensure that there have been no significant changes to the performance of the heating, ventilation, and air conditioning (HVAC) system. Airflow criteria are established during qualification studies.
测量风速是为了确保有足够的气流来保护暴露在外的产品、与产品接触的包装部件以及与产品接触的表面。测量风速也是为了确保暖通和空调系统的性能没有发生重大变化。气流标准是在确认研究期间制定的。

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Topic B.1: Airflow Visualization 主题 B.1：气流可视化

Problem Statement
问题陈述
What is the purpose of airflow visualization studies and how often should they be performed?
气流可视化研究的目的是什么？

Recommendation
建议
Airflow visualization studies should be used to evaluate airflow patterns in critical zones including Grade A and Grade B to ensure there is no ingress at interfaces from the surrounding environment. Such studies are recommended for the qualification of new or renovated facilities or of changes in facilities. In particular, airflow visualization studies should be done during qualification studies, and the studies should be repeated when any significant changes are made that might have an impact on study results (e.g., changes to air-handling systems, aseptic processing equipment, HEPA filters, air return risers/outlets, effectiveness of barrier systems, such as restricted access barrier system (RABS) doors) and after periodic intervals that are consistent with the capabilities and level of process monitoring of the air-handling system. Such an impact should be evaluated following applicable change- management procedures.
气流可视化研究应用于评估包括 A 级和 B 级在内的关键区域的气流模型，以确保边缘区域不会受到来自背景环境的侵入污染。建议对新增、改造或变更后的设施进行此类研究。特别是在确认研究期间应进行气流可视化研究，并且当进行任何可能影响研究结果的重大变更时（例如，更改空气处理系统、无菌工艺设备、HEPA 过滤器、空气回风升降管/出口、屏障系统的有效性，如受限制的进入屏障系统（RABS）门）应重复进行研究，并按照空气处理系统的监测能力和级别进行持续的周期确认。这种影响应该按照适用的变更管理程序进行评估。

For Grade A airflow, visualization studies should also be performed to assess if new and current interventions are in compliance with good aseptic working principles. Evaluation of these interventions should show that they are appropriate to meet first-air principles. These interventions should then be simulated and assessed in aseptic process simulation (APS) runs, and finally be included in the list of authorized interventions.
对于 A 级气流，还应进行可视化研究，以评估新的和当前的干预措施是否符合良好的无菌操作规范。对这些干预措施的评估应表明它们符合首过气流原则。然后，应在无菌工艺模拟（APS）执行中对这些干预措施进行模拟和评估，并最终将其纳入许可的干预措施清单。

Airflow visualization studies can also be used for investigative purposes (e.g., in cases of contamination) and can be very effective training tools. The outcome and approval of airflow visualization studies should be documented.
气流可视化研究也可用于调查目的（如在污染情况下），并可作为非常有效的培训工具。需有文件证明气流可视化研究的结果和批准。

Visualized airflow patterns should be executed in operational (dynamic) conditions to understand the impact of moving parts and personnel interventions on the actual airflow. In situ air-pattern analysis should be conducted at the critical zones to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. Studies should also be used in less critical zones to verify flow from

cleaner to less-clean areas (EU Annex 1, Section 4.15). Airflow visualization studies should be accompanied by a thorough analysis of the results and appropriate corrective action, including possible redesign of facility, equipment, or interventions, if indicated. Studies are valuable for informing the overall CCS, such as a facility's environmental monitoring (EM) programs and the design of interventions and in support of the training program.

应在运行（动态）条件下执行可视化气流模型研究，以了解运动部件和人员干预对实际气流的影响。应在关键区域进行现场气流模型分析，以证明在动态条件下产品上方和周围受到单向气流和清洁防护。还应在非关键区域进行研究，以确证气流从清洁度较高的区域流向清洁度较低的区域（欧盟附录 1 第 4.15 节）。在进行气流可视化研究的同时，应对研究结果进行全面分析，并采取适当的纠正措施，包括对设施、设备或干预措施进行可能的重新设计（如有必要）。研究对于整个 CCS 都很有价值，如制定设施环境监测（EM）计划、设计干预措施以及用于支持培训计划。

Because this is a disruptive activity for aseptic areas, proper care and adequate technologies should be used to prevent deterioration or contamination of the cleanroom and the equipment installed. A procedure should be established to ensure proper sanitization and cleanliness of the cleanroom after execution of the airflow study.

由于这对无菌区域是一项破坏性活动，因此应通过恰当的防护以及适配的技术来防止洁净室和所安装设备的受到损坏或污染。应制定一套程序，确保在气流研究结束后需对洁净室进行适当的消毒和清洁。

The decision and frequency of repeated air visualization studies should be based on a risk assessment of the process and capabilities of the air system. Even where no changes are believed to have occurred in the cleanroom or aseptic processing activities and where monitoring indicates that the airflow remains in a state of control, it is prudent to consider periodic air visualization studies to assure that process variables have not adversely affected airflow performance. Improvement in airflow visualization technology may also warrant repeat of airflow visualization studies.

应基于对工艺和空气系统能力的风险评估来决定是否需要重复进行空气可视化研究以及重复研究的频率。即使洁净室或无菌加工活动未发生变化，且监测显示气流仍处于受控状态，也应谨慎考虑定期进行气流可视化研究，以确保工艺变量未对气流性能产生不利影响。气流可视化技术的改进也可能需要重新进行气流可视化研究。

Rationale

理由

First-air flushing of exposed products, product-contact packaging components, and product-contact surfaces is critical to ensure adequate protection from contamination. Airflow patterns are established during qualification studies and are assessed in response to changes to ensure that the qualified conditions have not changed. Their visualization allows evaluation of their adequacy for this purpose: multiple-angle recording may be necessary for an adequate visualization in the environment. (See also Section I, Topic B.2: Airflow Visualization Recording.) The amount of time between air visualization studies should not be excessive because the accuracy and usefulness of those studies may be impacted. For example, where that period of time exceeds 5 years, additional justification for that length of time may be necessary.

暴露产品、产品接触包装组件和产品接触表面进行首过空气吹扫对于确保充分保护免受污染至关重要。在确认研究期间建立气流模型后，过程中产生的变更需进行评估，以确保确认状态未发生改变。其可视化结果允许评估其是否适合此目的：在环境中进行充分可视化可能需要多角度记录。（另见第 I 部分，主题 B.2：气流可视化记录。）空气可视化研究之间的时间不应过长，因为这些研究的准确性和有效性可能会受到影响。

例如，如果这段时间超过 5 年，可能需要为这段时间提供额外的说明。

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Topic B.2: Airflow Visualization Recording

主题 B.2：气流可视化记录

Problem Statement
问题陈述
Should airflow visualization studies be recorded?
是否应记录气流可视化研究?

Recommendation
建议
Airflow visualization studies should be recorded (typically by video), and the review and approval of the video recording should be documented and retained. Written conclusions should be reported to describe the outcomes of these tests. Preferably, the source of smoke generation should cause minimal contamination of the area. The quantity of smoke generated should be appropriate for the size of the area being evaluated and sufficient to clearly discern the airflow pattern. The impact of operator intervention and equipment operation during aseptic processing should be investigated during airflow visualization studies.
气流可视化研究应进行记录（通常是通过录像），录像的审核和批准结果应记录并归档。应提供书面报告形式的结论来说明这些测试的结果。最好将烟雾产生源对区域造成的污染降至最低。产生的烟雾量应经过评估，需要与区域的大小相适应并足以清楚地辨别气流模型。在气流可视化研究中应观察无菌加工过程中操作员干预和设备操作的影响。

Multiple angles may be needed to provide an accurate representation of airflow.
可能需要多个角度录像来提供准确的气流表现形式。

Video recordings are electronic data and must be retained and maintained accordingly. Records of airflow visualization studies should also be used as training material for personnel operating in cleanrooms, for example, to help them visualize the impact of any aseptic manipulation on the airflow and on the risk of contamination.
视频记录属于电子数据，因此必须保留和维护。气流可视化研究记录也应作为洁净室操作人员的培训材料，例如，帮助他们直观地了解所有无菌操作对气流和污染风险的影响。

Rationale
理由
Airflow patterns are studied to indicate adequate protection of exposed products, product-contact packaging components, and product-contact surfaces. Airflow patterns are established during qualification studies for evaluating, and thereby ensuring, proper airflow patterns. The patterns should be documented so that changes can be identified. Video recordings or records from another visualization technique must show airflow patterns with adequate definition and clarity as regards the flow in the three-dimensional environment. Due to the fact that video recordings provide a two- dimensional visualization, multiple angles may be needed to provide an accurate representation of three-dimensional airflow visualization.
对气流模型进行研究，以显示对暴露产品、产品接触包装部件和产品接触表面的充分保护。气流模型是在确认研究期间建立，并用于评估确保该气流模型可提供适当的防护作用。应记录该气流模型，以便识别变化。

视频记录或其他可视化技术的记录必须有足够的清晰度和准确度显示气流在三维环境中的流动模式。由于视频记录提供的是二维可视化效果，因此可能需要多个角度才能准确呈现三维气流可视化效果。

Recordings allow for additional evaluation of the study at any successive time, by employees who did not participate in their execution, and for training purposes.
记录允许未参与执行研究的人员在任何相继的时间点对研究进行额外的评价，用于培训。

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Topic C: Grade A Environment Over Cappers

主题 C：轧盖机 A 级环境

Problem Statement
问题陈述
What are the recommended environmental conditions for capping aseptically processed, stoppered vials when the capping takes place outside of a Grade A environment?
在 A 级环境之外为无菌处理的西林瓶轧盖时，建议的环境条件是什么？

Recommendation
建议
When capping is undertaken as a clean process outside a Grade A environment, a Grade A air supply over the capping machine is sufficient, provided validated automatic checks for all the vials (e.g., using a missing/raised stopper detector) are in place immediately prior to, or in front of, the capping station to reject any vials with stoppers that do not remain properly seated before they enter the capping and sealing station. The HEPA filters used should be requalified periodically as described in **Section I, Topic E**: Testing of HEPA Filters.
当轧盖操作在一个 A 级的洁净环境之外进行时，只要在轧盖上提供 A 级的空气供应，并在轧盖工位前或轧盖机前设置有效的自动检测装置（例如使用瓶塞缺失/凸起检测器）以剔除任何在进入轧盖机之前瓶塞未正确就位的小瓶。所使用的高效过滤器应按照**第 I 部分主题 E**：高效过滤器的测试中的说明定期重新确认。

Monitoring requirements for total particulate and microbiological contamination at the capping machine outside the aseptic core should be defined by the company following a risk assessment.
公司应通过风险评估，确定对无菌核心之外的轧盖机上的悬浮粒子数和微生物污染的监控要求。

NOTE: EU Annex 1 states that when vial capping is undertaken as a clean process outside the aseptic core, stoppered vials should be protected with a Grade A air supply until the cap has been crimped. It also states that RABS and isolators may be beneficial in assuring the required conditions.
注：欧盟附件 1 规定，当西林瓶轧盖作为无菌核心之外的洁净工艺进行时，应使用 A 级气源保护已封口的西林瓶，直至盖子压紧。它还指出，RABS 和隔离器可能有助于提供所需的条件。

Rationale
理由
A properly seated stopper represents an adequately sealed container and a microbiological barrier. Therefore, efforts should be taken to ensure that the container is maintained under conditions that will not add contamination until it is properly stoppered prior to capping. When there is a risk that the stopper might be raised prior to capping, steps should be taken to reject those vials.
塞子正确就位代表容器已充分密封并具有微生物屏障作用。因此，应努力确保容器保持在不会增加污染的条件下，直至在轧盖之前盖好瓶塞。如果瓶塞有可能在轧盖前被提起，则应采取措施剔除这些小瓶。

A qualified aseptic filling process includes assurance of the proper routine placement of stoppers, as aligned with container closure integrity requirements. A missing or raised stopper-detector must be qualified and

challenged on a routine basis and units with compromised or non-integral stoppers should be rejected before capping.

合格的无菌灌装工艺包括确保塞子按照容器密封完整性的要求正确放置。瓶塞缺失/凸起检测器必须经过定期确认和检测，有受损或非完整塞子的装置应在轧盖前被剔除。

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Topic D: Differential Pressure 主题 D：压差

Problem Statement
问题陈述
What should be the air-pressure differential between zones of differing cleanliness classification (e.g., between Grade B and Grade C zones)?
不同洁净等级的区域（如 B 级和 C 级区域）之间的气压差应该是多少？

Recommendation
建议
Positive pressure between zones with different air cleanliness classifications should ensure airflow direction from the “cleaner” toward the “less clean” zones.
不同洁净等级区域之间的正压应确保气流从 "清洁度较高 "区域流向 "清洁度较低 "区域。

A prolonged zero-pressure differential between such zones, or a pressure reversal to the extent that the cleanliness of the environment is compromised, must be avoided.
必须避免这些区域之间出现长时间的零压差，或负压差以至于影响环境的清洁度。

A pressure differential between different classified zones of not less than 10 pascals (with doors closed) is commonly expected. However, because the principal purpose is to ensure that a minimum measurable positive pressure is maintained, other differential pressure levels may be required based on facility complexity, HVAC system design, and operational characteristics. Provisions may need to be made for containment for certain material types (e.g., sensitizing or hazardous materials). In such cases, alternative strategies, such as pressurized (negative or positive) airlocks, should be considered for which the primary emphasis is on material confinement to prevent transfer to other areas.
不同等级区域之间的压差通常不低于 10 帕斯卡（门关闭时）。不过，由于其主要目的是确保保持最小的可测量正压，因此可能需要根据设施的复杂性、暖通空调系统设计和运行特性来确定其他压差水平。对于某些类型的物料（如致敏物料或危险物料），可能需要进行密封处理。在这种情况下，应考虑采用其他策略，如加压（负压或正压）气闸，其主要重点是封闭物料，防止其转移到其他区域。

An appropriate pressure differential is principally maintained by interlocked and alarmed air locks and doors between the zones of different cleanliness levels and should be continuously monitored by differential pressure devices. Although brief periods of low- or zero-differential pressure may exist between an area and an air lock (of the same grade) with a door open, a measurable pressure differential should be maintained between areas (of different grades) separated by the air lock.
适当的压差主要通过不同洁净度等级的区域之间的具备联锁、警报功能的气闸和门来维持，并应通过不同的压力装置进行持续监控。虽然在门打开的情况下，一个区域和一个气闸（同一等级）之间可能会存在短暂的低压差或零压差，但在被气闸隔开的区域（不同等级）之间应保持可测量的压差。

An alarm strategy with appropriately qualified alarm delay limits should be defined for changes to differential pressure and/or pressure drops and should be underpinned by quality risk management. Transient low- or zero-differential pressure occurrences represent critical alarm functions, and these alarms must indicate airflow inversions that are assessed to pose a risk to cleanliness of the area.

应以质量风险管理为基础针对压差和/或压降的变化制定具有适当报警延迟限制的报警策略。瞬时低压差或零压差的报警出现表示为关键的警报功能，这些警报必须表明气流倒灌被评估为对区域的洁净度构成风险。

Inversion of airflow may be rectified by such steps as:
气流倒转可通过以下步骤进行纠正：

- Room balancing (e.g., volume of air and differential pressure adjustments in adjacent rooms) and air-exchange rate of the room
  房间平衡（如相邻房间的风量和压差调整）和房间换气次数调整
- Changes in sequence and/or timing of door openings
  改变开门顺序和/或开门时间
- Process and cleanroom design (use of interlocks)
  工艺和洁净室设计（使用联锁装置）
- Clearing obstructions from air returns
  清除回风口的障碍物

Airflow visualization studies and/or ingress challenges should be included to verify the maintenance of a proper cascade from cleaner to dirtier zones and to prove there is an outward airflow when doors are open between adjacent rooms.
应包括气流可视化研究和/或入口挑战，以验证从洁净度较高区域到洁净度较低区域能够保持适当的气流倾泻，并证明相邻房间之间的门打开时存在向外的气流。

NOTE: Positive differential pressure between rooms of the same classification, where one room is considered cleaner than an adjacent room of the same classification, should also be considered (e.g., wash areas that are Grade C and are peripheral to non-wash Grade C areas). In such cases, a lower differential pressure can be appropriate.
注：同一等级的房间之间也应考虑正压差，即一个房间比相邻的同一等级房间更清洁（例如，C 级清洗区与 C 级非清洗区相邻）。在这种情况下，可以适当降低差压。

Rationale
理由
The primary objective of differential pressure is to maintain a cascade (i.e., positive pressure between zones of different air cleanliness classifications) to ensure that air flows from the cleaner to the dirtier zone.
压差的主要目的是保持气流倾泻（即在不同空气洁净等级的区域之间保持正压），以确保空气从较清洁的区域流向较脏的区域。

Differential pressure is necessary to ensure that the direction of airflow between adjacent, connected areas of different air cleanliness classifications is only from the higher-grade to lower-grade areas. Maintaining room air-pressure differentials requires that appropriate volumes of air per unit of time be supplied to the various classified environments. This, in turn, has an impact on the numbers of air changes and supply velocities. Data (e.g., from airflow visualization studies and physical measurements) should be available to support the adequacy of the chosen pressure differentials.
为了确保不同空气洁净度等级的相邻、相连区域之间的气流方向只能从高等级区域流向低等级区域，压差是必要的证明手段。要保持室内空气压差，就必须在单位时间内向不同等级的环境提供适当的风量。这反过来又会影响换气次数和风速。所以应通过数据（如气流可视化研究和物理测量数据）来证明所选压差的合理

性。

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Topic E: Testing of HEPA Filters 主题 E：高效过滤器的测试

Problem Statement
问题陈述
What is the frequency with which HEPA filters should be tested?
高效过滤器的检测频率是多少?

Recommendation
建议
HEPA-filter testing should comprise integrity testing, airflow volume measurement, and airflow velocity testing. HEPA filters should be tested minimally upon initial installation and replacement. Requalification frequency should be based on a risk assessment using historical performance, available data, cleanroom design, and usage.
高效过滤器测试应包括完整性测试、风量测试和风速测试。高效过滤器至少应在初次安装和更换时进行测试。再确认频率应根据历史性能、可用数据、洁净室设计和使用情况进行的风险评估确定。

HEPA-filter performance characteristics for Grade A (and surrounding Grade B) areas should be requalified at a maximum interval of six months. For lower-grade areas (Grades C, Grade D, and remaining Grade B areas not required to be supplied with unidirectional airflow), a maximum interval of 12 months applies. The airflow velocity testing may be replaced with recovery testing. The frequency of recovery testing in these lower grade areas should be determined based on risk assessment.
A 级（及周围的 B 级）区域的高效过滤器性能特征应最长每隔 6 个月重新确认一次。对于较低等级的区域（C 级、D 级和其余不需要提供单向气流的 B 级区域），最长间隔时间为 12 个月。风速测试可由恢复测试取代。在这些低等级区域进行恢复测试的频率应根据风险评估来确定。

In lower-grade areas where airflow is unidirectional the air velocity testing should be based on risk assessment.
在低等级的单向流区域，风速测试应基于风险评估。

Production campaigns should be scheduled to allow for requalification. Where exceptions occur that result in a delay in a periodic requalification, the requalification should be performed as soon as possible after the delay and the risk of such a delay on product quality should be evaluated.
应安排生产活动以进行再确认。如果出现异常情况，导致定期再确认延迟，则应在延迟后尽快进行再确认，并评估此类延迟对产品质量的风险。

Where testing indicates a HEPA filter integrity or performance failure, steps should be taken to repair or replace the filter, or otherwise address the failure, and steps should also be taken to address product impact from the failure.
如果测试表明 HEPA 过滤器存在完整性失败或性能故障，则应采取措施维修或更换过滤器，或以其他方式解决故障，还应采取措施解决故障对产品的影响。

Rationale
理由
Because routine monitoring is not sensitive enough to assure the performance of the HEPA filter system or

individual HEPA filters, periodic retesting of the HEPA-filter system and individual HEPAs is beneficial, as reflected in EU Annex 1 and other health authority guidances.

由于常规监测不够灵敏，无法确保 HEPA 系统或单个 HEPA 的性能，如欧盟附录 1 和其他卫生当局指南所示，定期对高效空气过滤器和单个高效空气过滤系统进行重新测试是有益的。

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Topic F: HEPA Filter Patching 主题 F：高效过滤器修补

Problem Statement
问题陈述

Can HEPA filters be patched? If so, what is the maximum allowable patch size?
高效过滤器是否能被修补？如果可以，允许的最大修补尺寸是多少？

Recommendation
建议

HEPA-filter patching for Grade A should be avoided. HEPA-filter patching for Grade B-D should proceed only after the repair is justified by careful risk assessment, the repair is performed to industry standards to ensure patch durability, and aseptic process production should only commence after the performance of the repaired HEPA-filter has been verified to show that it has returned to a qualified state. Testing should include leak and velocity testing. If the testing does not verify that the repaired HEPA has returned to a qualified state, then the HEPA should be repaired if possible or replaced.
A 级高效过滤器是不允许进行修补的。B 级至 D 级高效过滤器只有在以下情况下方可进行修补：通过仔细的风险评估证明修复是合理的；按照行业标准进行修复，以确保修补的耐用性；只有在对修复后的高效过滤器的性能进行确认，证明其已恢复到合格状态后，才能开始无菌工艺生产。测试应包括检漏和风速测试。如果测试不能证实修复后的高效过滤器已恢复到合格状态，则应尽可能修复或更换高效过滤器。

HEPA filters can be repaired or patched, but the company should develop a rationale for allowable filter repair shape and size fit for the different installation and area classifications based on a thorough risk assessment.
高效过滤器可以进行修复或修补，但公司应在进行彻底风险评估的基础上，针对不同安装位置和区域级别，制定合适的允许过滤器修复的形状和尺寸的基本原则。

If this rationale supports repair, HEPA filters may be patched with room-temperature vulcanization silicone or other suitable material as long as filter integrity is restored and the airflow volume and velocity through the filter are not significantly affected (i.e., room pressure differentials and airflow patterns remain as validated).
如果这一原则支持修复，只要过滤器的完整性得到恢复，并且通过过滤器的风量和速度不会受到显著影响（即，房间压差和气流模式仍保持验证状态），那么可以用室温硫化硅树脂或其他合适的材料修补 HEPA 过滤器，。

Based on the different performance requirements for filters in different grades and different installations, one of the practices listed below may be followed. After repairs are made, additional testing is needed to ensure that the filter meets the performance requirements.
根据不同等级和不同装置的过滤器的不同性能要求，可采用以下做法之一。修复后，需要进行额外的测试，以确保过滤器符合性能要求。

International Environmental Sciences and Technology (IEST)-recommended practice (RP)- CC001.5 states, “Unless otherwise specified, the medium of filter units to be used in cleanroom or clean-air device applications may be patched with medium or adhesive, not to exceed an area of 13 cm^2 (2 in^2) in any one patch, or a total of 1% of the area being patched.”
国际环境科学与技术（IEST）-推荐做法（RP）-CC001.5 规定，“除非另有规定，洁净室或清洁空气设备应用

中使用的过滤装置的介质可以用媒介或粘合剂进行修补，任何单一修补面积不得超过 13 cm^2（2 in^2），或修补总面积不得超过被修补面积的 1%。”

European Standard EN ISO 29463-4 states, “A filter may be repaired if necessary and shall then be retested… All repairs together (including those made by the filter manufacturer) shall not block or restrict more than 0.5% of the filter face area (not including the frame) and the maximum length of each single repair shall not exceed 3.0 cm.”
欧洲标准 EN ISO 29463-4 规定："如有必要，可对过滤器进行维修，然后应重新进行测试……所有维修（包括过滤器制造商进行的维修）堵塞或限制的面积不得超过过滤器表面积（不包括框架）的 0.5%，且每次维修的最大长度不得超过 3.0 厘米"。

IEST RP-CC034.5 states, “Field repair should not block or restrict more than an additional 3.0% of the filter face area, and no single repair should have a lesser dimension exceeding 3.8 cm (1.5 in.).”
IEST RP-CC034.5 规定："现场修复时，阻塞或限制的面积不应超过额外 3.0% 的过滤面面积，且任何单个修复的较小尺寸都不应超过 3.8 厘米（1.5 英寸）"。

ISO 14644-3, Section B.6.6, allows for repairs and repair procedures “by agreement between the customer and supplier.”
ISO 14644-3 第 B.6.6 节允许 "由客户和供应商商定 "维修和维修程序。

Rationale
理由

Industry standards and recommendations, as listed in the above recommendation, support the limited use of proper repair techniques to maintain the integrity and performance of cleanroom HEPA filters. However, this practice should be evaluated on a product risk basis because new HEPA filters are preferable to repaired filters for more critical operations. If the repaired HEPA filter performs to qualification standards, then that performance should be sufficient to allow its continued use.
上述建议中列出的行业标准和建议支持有限度地使用适当的维修技术来保持洁净室 HEPA 的完整性和性能。不过，这种做法应根据产品风险进行评估，因为对于更关键的操作而言，新的高效过滤器比维修过的过滤器更可取。如果修复后的高效过滤器能达到合格标准，那么这种性能就足以允许继续使用。

NOTE: EU Annex 1 requires precautions when carrying out this type of intervention, such as restricting access to the work area, clearly defining work protocols, and cleaning, disinfecting, and environmental monitoring being considered.
注：欧盟附录 1 要求在进行此类干预时采取预防措施，如限制进入工作区，明确规定工作规程，并考虑进行清洁、消毒和环境监测。

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Topic G: Laminar Versus Unidirectional Airflow

主题 G：层流与单向流

Problem Statement
问题陈述

Should airflow in Grade A critical zones be laminar or unidirectional?
A 级关键区的气流应该是层流还是单向流?

Recommendation
建议

Airflow in critical Grade A zones (i.e., where products or sterile components are exposed) should be unidirectional. In aseptic processing, unidirectional airflow means that the air mass flows from the source (i.e., the HEPA filter) in one direction into or over the critical zone and its contents in such a way as to ensure that the exposed products and sterile components are always in air that has not passed any other component, operator, or equipment that has not been sterilized. This is the concept of first air.
A 级关键区（即产品或无菌部件暴露的地方）的气流应是单向流。在无菌处理过程中，单向气流是指气流从源（即 HEPA 过滤器）单向流入或流过关键区域及其内容物，以确保暴露的产品和无菌组件始终处于未经过任何其他组件、操作员或未灭菌设备的空气中。这就是初始气流的概念。

NOTE: In closed isolators, turbulent flow may be acceptable for Grade A zones when it is supported by operational qualification demonstrating the maintenance of acceptable particulate levels.
注：在封闭式隔离器中，A 级区可以接受湍流，但必须有操作确认证明可以维持可接受的微粒水平。

Rationale
理由

The term “laminar,” although used historically in this context, is problematic. True laminar airflow is virtually impossible to achieve in physical environments. Moreover, true laminar airflow is not necessary to achieve appropriate airflow that maintains the first-air concept.
“层流 "一词虽然历来用于此类语境中，但却存在问题。真正的层流气流在物理环境中几乎不可能实现。此外，真正的层流气流并不是实现保持初始气流概念的适当气流的必要条件。

ISO 14644-3:2019 defines unidirectional airflow as “controlled airflow through the entire cross- section of a clean zone with a steady velocity and approximately parallel streamlines.”
ISO 14644-3:2019 将单向气流定义为 "以稳定的速度和近似平行的流线通过洁净区整个横截面的受控气流 "。

The first-air approach applies to all airflow situations and aseptic processing methods where contamination through airborne means might be a risk.
初始气流方法适用于所有气流情况和无菌加工方法，通过空气传播的污染可能是一种风险。

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Topic H: Length and Radii of Airborne Sampling Tubing

主题 H：空气采样管的长度和半径

Problem Statement
问题陈述
How should tubing for total particulate sampling be configured?
总颗粒物采样管道应如何配置？

Recommendation
建议
The sample tubing length and number of bends should be minimized. Bend radii should be maximized in accordance with the recommended practices from the equipment manufacturer and should be technically justified. Tubing with bends should be sized so that the bend radii do not change.
应尽量减少样品管的长度和弯曲次数。弯曲半径应根据设备制造商推荐的方法尽可能做到最大，并应在技术上进行论证。应确定弯管的尺寸，确保弯曲半径不会改变。

Rationale
理由
Each unique particle size will have a different deposition profile in tubing based on, for example, airflow velocity and sample volume, tubing diameter, sampling port arrangement, temperature, bend radius, tube length, and tubing material. Because it is a range of sizes (e.g., 0.5 microns and greater in optical diameter) that particulate monitoring attempts to assess, no single set of radii or length conditions can describe best practices for each of these particle sizes. Minimizing the number of tubing bends, maximizing radii, and minimizing overall tubing length should be the goal and should be done in accordance with the particle-counter equipment manufacturer's recommended best practices.
根据气流速度和采样体积、管道直径、采样口布置、温度、弯曲半径、管道长度和管道材料等因素，每种独特大小的颗粒在管道中都会有不同的沉积曲线。由于微粒监测试图评估的是一系列粒度（如光学直径 0.5 微米及以上），因此没有一套单一的半径或长度条件可以描述每种粒度的最佳做法。减少管道弯曲次数、尽量增大半径和尽量缩短管道总长度应该是我们的目标，并且应该按照颗粒计数器设备制造商推荐的最佳实践来进行。

The particle-counter equipment manufacturer should provide a technical justification for its recommendations. Instrument calibration should address sampling configuration.
粒子计数器设备制造商应提供其建议的技术理由。仪器校准应针对采样配置。

NOTE: EU Annex 1 now states that tube length should typically be no longer than 1 m.
注：欧盟附录 1 现在规定，管道长度一般不应超过 1 米。

NOTE: ISO 14644-1:2015 also states that tube length should be no longer than 1 m.
注： ISO 14644-1:2015 也规定，管道长度不应超过 1 米。

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Topic I: RABS and Isolators—Aseptic Processing Technologies

主题 I：RABS 和隔离器--无菌加工技术

Problem Statement
问题陈述

What "barrier" systems and practices should be used to reduce the risk of microbiological contamination from human intervention and external environment in aseptic processing systems?
在无菌加工系统中，应采用哪些 "屏障"系统和做法来降低人为干预和外部环境造成微生物污染的风险？

Recommendation
建议

Barrier systems should be used for aseptic processes. Barrier methods typically include isolators and RABS but may also include other technologies where physical separation is achieved. The systems and controls associated with the design and use of barrier systems should be included in the CCS.
无菌工艺应使用屏障系统。屏障方法通常包括隔离器和 RABS，但也可包括实现物理隔离的其他技术。与屏障系统的设计和使用相关的系统和控制措施应纳入 CCS。

Barrier systems are defined as "closed" or "open", based on exposure to the surrounding environment. While all isolators and RABS provide a barrier from personnel and the external environment, closed isolators provide a higher level of protection with respect to open isolator systems and RABS, which require additional precautions and controls to prevent contamination.
根据与周围环境的接触情况，隔离系统被定义为 "封闭式"或 "开放式"。虽然所有隔离装置和 RABS 都能阻隔人员和外部环境，但相对于开放式隔离装置和 RABS，封闭式隔离装置能提供更高级别的保护，因为开放式隔离装置和 RABS 需要额外的预防措施和控制来防止污染。

Isolators differ from RABS because they usually have automated decontamination systems, employ continuous HEPA-filtered air differential/over-pressure control, are physically sealed from the external environment or, in the case of open isolators, have positive airflow at the product exit and have doors or panels that cannot be opened for any reason during the aseptic process without repeating the decontamination process. As such, isolators should provide a higher level of protection compared to RABS which, in turn, provides a higher level of protection compared to classical curtained manual aseptic processing.
隔离器不同于 RABS，因为它们通常有自动净化系统，采用连续的 HEPA 过滤空气压差/过压控制与外部环境保持物理密封，或者，对于开放式隔离器，在产品出口处有正压气流，以及在无菌处理过程中不能以任何理由打开的门或面板，否则将重复净化过程。因此，隔离器应比 RABS 提供更高水平的保护，而 RABS 又比传统的帘式手工无菌处理提供更高水平的保护。

Design and Operation
设计和运行

Isolators and RABS should be designed and operated in such a way as to reduce the risk of microbiological contamination to critical operations, including transfer of materials and components, EM, setup of filling systems, removal of fallen containers or components, fill checks, or other interventions within these systems.
隔离器和 RABS 的设计和操作应能降低关键操作受到微生物污染的风险，包括材料和部件的转移、环境监

控、灌装系统的安装、移除掉落的容器或部件、灌装检查或对这些系统的其他干预。

The following should be considered for the design and operation of isolators and RABS:
隔离器和 RABS 的设计和运行应考虑以下因素：

- Open isolators may be placed in Grade C environments. Closed isolators may be placed in Grade D environments. RABS should be placed in Grade B environments only. The decontamination and transfer of materials into and out of the isolator and RABS should be qualified, controlled, and monitored to prevent contamination of materials and sterile product.
  开放式隔离器可置于 C 级环境。封闭式隔离器可放置在 D 级环境中。RABS 只能放置在 B 级环境中。隔离器和 RABS 的除污和材料传入传出应进行确认、控制和监测，以防止材料和无菌产品受到污染。
- The design should facilitate uncomplicated aseptic setup of the filling line and should negate the need for any contact to critical surfaces (e.g., filling needles) via operator gloves or RABS/isolator gloves and should provide for first-air principles to be maintained within the critical zone.
  设计应便于灌装线的无菌安装，并应避免通过操作员手套或 RABS/隔离器手套接触关键表面（如灌装针头），应在关键区域内保持初始气流原则。
- Direct contact of critical surfaces by RABS/isolator gloves should be avoided.
  应避免 RABS/隔离器手套直接接触关键表面。
- The location of glove ports and gloves in isolators and RABS should be designed to facilitate effective and easy performance of interventions by all personnel. Their location and design should provide for first-air protection in the critical zone and should not present an ergonomic challenge to operators that may otherwise result in suboptimal, or a lapse in, aseptic technique during operations.
  隔离器和 RABS 中手套口和手套的位置设计应便于所有人员有效、轻松地进行干预。它们的位置和设计应为关键区域提供初始气流保护，并且不应给操作人员带来人体工程学方面的挑战，否则可能导致操作过程中无菌技术不达标或失效。
- Glove ports, gloves, and transfer ports should remain integral after decontamination and throughout the operation and should be tested regularly for leaks.
  手套口、手套和传输口在净化后和整个操作过程中都应保持完整，并应定期检测是否有泄漏。
- Gloves should be designed and positioned to avoid damage.
  手套的设计和位置应避免损坏。
- The interior of the isolator and RABS, including the positioning of glove ports, gloves, and other equipment, should be designed to facilitate effective decontamination and transfer/movement of materials and product.
  隔离器和 RABS 的内部设计，包括手套口、手套和其他设备的位置，应便于有效地清除污染和转移/移动物料和产品。
- Isolator and RABS decontamination methods should be validated and controlled to render sur- faces and items incapable of contaminating the environment or sterile product.
  隔离器和 RABS 净化方法应经过验证和控制，使表面和物品无法污染环境或无菌产品。
- Controls should be in place to maintain a decontaminated state of interior, environment, and materials.
  应采取控制措施，保持隔离器和 RABS 内部、环境和材料的净化状态。
- The decontamination method should not chemically contaminate or otherwise compromise materials.

净化方法不得对材料造成化学污染或其他损害。

- Equipment and isolator and RABS should be designed to work with operational procedures and aseptic techniques to minimize the need for interventions.
  设备、隔离器和 RABS 的设计应与操作程序和无菌技术相配合，以尽量减少干预的需要。

Intervention Control
干预控制

Proper aseptic techniques should be used to perform activities and interventions in the RABS/isolator. Interventions performed in isolators and RABS should be assessed for risk of contamination to product and should not be permitted if they present an unacceptable increased risk to the aseptic process.
在 RABS/隔离器中进行活动和干预时应使用正确的无菌技术。应评估在隔离器和 RABS 中进行的干预活动对产品造成污染的风险。

These interventions should be designed to allow for the performance of activities using proper aseptic techniques, including employing first-air principles and avoiding gloved contact with critical surfaces.
在设计这些干预措施时，应考虑到使用正确的无菌技术开展活动，包括采用初始气流原则和避免戴手套接触关键表面。

RABS should be designed and operated with doors and panels closed during aseptic processing. Interventions with open doors or panels should be avoided. Where possible, interventions performed in RABS should be performed with doors closed using fixed mounted gloves. Where not possible, interventions performed with open RABS doors should be limited and special controls and precautions should be used. It may be necessary to open RABS doors for some manual setup activities, using special controls and precautions.
RABS 的设计和操作应使门和面板在无菌处理过程中关闭。应避免敞开门或面板进行干预。在可能的情况下，RABS 中进行的操作应使用固定安装的手套在门关闭的情况下进行。在不可能的情况下，应对打开 RABS 门进行干预的情况进行限制，并应使用特殊控制和预防措施。对于打开 RABS 门进行的一些手动安装的活动，可能需要使用特殊控制和预防措施。

When processes require open-door interventions, those activities should be assessed for contamination risk, must be part of the qualified list of interventions, and must incorporate additional control measures based on the risk of microbiological contamination that these may produce.
当工艺需要开门干预时，应对这些活动进行污染风险评估，必须将其作为合格干预清单的一部分，并且必须根据这些活动可能产生的微生物污染风险增加控制措施。

Such additional control measures may include (but are not limited to):
这些增加的控制措施可能包括（但不限于）：

- Additional disinfection and sanitization of non-product-contact surfaces using a qualified disinfection agent and procedures, including the interior of doors and panels opened during the activity
  使用经确认的消毒剂和程序对非产品接触表面进行消毒和杀菌，包括在活动期间打开的门和面板的内部
- Door access with recorded intervention alarms or an effective means of documentation
  带有记录干预警报或有效记录手段的门禁系统

- Documented line clearance
  记录清场情况
- Positive airflow from the enclosure to the surrounding environment when the door is opened, which has been assessed and documented in smoke studies
  当门打开时，正压气流从内部区域流向周围环境，这已在烟雾研究中进行了评估和记录
- Additional monitoring of product-contact surfaces and interior environment in proximity to activity
  对产品接触表面和活动附近的内部环境增加监测
- Additional removal or testing of materials or products exposed to the intervention
  增加对接触干预措施的材料或产品的清除或测试
- Monitoring of operator gloves and sleeves immediately after the open-door intervention
  开门干预后立即监测操作员的手套和袖子
- Air visualization studies or other means to assure that the activity and intervention design allows for performance without disrupting first-air principles
  气流可视化研究或其他手段，以确保活动和干预设计能够在不破坏初始气流原则的情况下进行操作

Decontamination
去除污染

Direct product-contact surfaces, including product and holding vessels, should be sterilized using vali- dated methods and maintained in a sterile state, using qualified procedures, throughout production.
直接接触产品的表面，包括产品和盛放容器，应使用有效的方法进行灭菌，并在整个生产过程中使用经确认的程序保持无菌状态。

Indirect product-contact surfaces include surfaces that will contact sterilized surfaces that will later con- tact sterile product, for example, stopper bowls and tracks that directly contact stoppers. These indirect product-contact surfaces must be rendered free of microbiological contamination that can contaminate direct product-contact surfaces. Where possible, the means to render these surfaces free of microbiological contamination should be sterilization. Where that is not feasible, however, due to the design of the isolator or RABS or when the handling of sterilized parts presents an unacceptable risk, then a means to decontaminate the indirect-contact parts should be used employing a method that renders those surfaces free of microbiological contamination and thus incapable of contaminating sterile product. *PDA Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators* suggests some means to do so (see Topic 6: Material Transport and Loading of Isolators).
产品间接接触表面包括与灭菌表面接触的表面，这些表面随后将与无菌产品接触，例如瓶塞料斗和与瓶塞直接接触的轨道。这些与产品间接接触的表面必须避免微生物污染，因为微生物污染会污染与产品直接接触的表面。在可能的情况下，应采取灭菌的方式使这些表面不受微生物污染。但如果由于隔离器或 RABS 的设计原因而无法做到这一点，或处理灭菌部件会带来不可接受的风险，则应采取措施消除间接接触部件的污染，以使这些表面不受微生物污染，从而无法污染无菌产品。*PDA 《隔离器中无菌药品无菌处理的注意事项》*提出了一些方法（见主题 6：隔离器的材料运输和装载）。

All interior non-product-contact surfaces, including glove ports, gloves, equipment, transfer ports, container transfer systems, and equipment surfaces should be decontaminated using validated methods that prevent microbiological contamination of product and do not compromise the quality of product.
所有内部非产品接触表面，包括手套口、手套、设备、转移口、容器转移系统和设备表面，都应采用有效的

方法进行净化，以防止产品受到微生物污染，并不影响产品质量。

Glove ports and gloves should be designed and positioned to avoid damage or loss of integrity during operation. Glove integrity should be monitored frequently, normally at the end of production and after the performance of interventions or activities that may pose a risk to glove integrity.
手套口和手套的设计和定位应避免在操作过程中损坏或丧失完整性。应经常监测手套的完整性，通常是在生产结束时以及在进行可能对手套完整性构成风险的干预或活动之后。

Failure Investigation
失败调查
Personnel can still be the source of contamination in isolators and RABS if the process or equipment design is flawed or if activities are not performed properly. However, because isolators and RABS reduce the risk of personnel as the source of contamination, special consideration should also be given to other potential sources of contamination. This includes system and process design, cleaning and disinfection procedures, decontamination process, and proper transfer procedures and material integrity, when investigating and evaluating critical-zone EM excursions, sterility-test failures, and APS failures.
如果工艺或设备设计有缺陷，或活动执行不当，人员仍可能成为隔离器和 RABS 中的污染源。不过，由于隔离器和 RABS 降低了人员作为污染源的风险，因此还应特别考虑其他潜在的污染源。在调查和评估关键区环境监测漂移、无菌测试失败和 APS 失败时，这包括系统和流程设计、清洁和消毒程序、净化流程以及适当的转移程序和材料完整性。

Rationale
理由
Personnel are a significant source of microbiological contamination and, therefore, are a risk to product sterility. Efforts to separate personnel from sterile products and product-contact surfaces reduce the risk of microbiological contamination. Barrier systems, such as isolators and RABS provide a physical separation between personnel, external environment, and exposed product or product-contact surfaces that help prevent microbiological contamination of the sterile product from personnel and the environment. For this reason, they provide more preventive controls and protection than conventional aseptic processing lines located in cleanrooms.
人员是微生物污染的一个重要来源，因此也是产品无菌的一个风险。努力将人员与无菌产品和产品接触面隔离，可降低微生物污染的风险。隔离器和 RABS 等屏障系统可在人员、外部环境和暴露的产品或产品接触表面之间进行物理隔离，有助于防止人员和环境对无菌产品造成微生物污染。因此，与位于洁净室中的传统无菌加工生产线相比，它们能提供更多的预防性控制和保护。

When designed and used properly, these systems can reduce or eliminate direct human interactions. However, these systems can be confining, restrict personnel movement, are complex, and are challenging to decontaminate and operate. Consequently, for these systems to be effective, they must be designed and operated correctly. Risk assessments can help to identify where additional control measures and design features are needed.
如果设计和使用得当，这些系统可以减少或消除人员干预活动。但是，这些系统可能会有局限性，限制人员行动，十分复杂而且在净化和操作方面具有挑战性。因此，要使这些系统有效，就必须正确设计和操作这些系统。风险评估可以帮助确定哪些地方需要额外的控制措施和设计特点。

The interior of these systems, including fixed gloves, are decontaminated, and not necessarily sterilized. Therefore, there is a need for proper equipment design, qualified cleaning procedures and use of aseptic technique and first-air principles, and the avoidance of contact with critical surfaces when performing activities and interventions.
这些系统的内部，包括固定手套，是经过净化的，不一定是经过灭菌的。因此，有必要进行适当的设备设计、合格的清洁程序、使用无菌技术和初始气流原则，以及在进行活动和干预时避免接触关键表面。

Barrier systems rely on the integrity of the barriers to prevent contamination. Therefore, the design and maintenance of transfer systems, procedures, and glove-integrity are essential.
屏障系统依靠屏障的完整性来防止污染。因此，转移系统、程序和手套完整性的设计和维护至关重要。

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Topic J: Environmental Clean-Up Period Determination (at Rest)

主题 J：环境自净时间的确定（静态）

Problem Statement
问题陈述

How much time is needed to reestablish acceptable cleanroom conditions after disruption of these conditions?
在这些条件被破坏后，需要多少时间才能恢复可接受的洁净室条件?

Recommendation
建议

The particle levels for the “at-rest” state should be achieved after a “clean-up” period, one that is sufficiently long to allow enough air turnover to return to qualified conditions, that has been established through qualification activities, and is controlled via established procedures.
"静态"状态下的粒子水平应在 "自净"时间后达到，"自净"时间应足够长，以便有足够的空气交换来恢复到通过确认活动确定的合格状态，并通过既定程序加以控制。

The best approach for this concept is not a time limit but, rather, a pre-established program of steps and measures to be taken in the event of a deviation in the CCS. This program should not be a de- scription of what to do but, rather, of what to consider when returning an environment to a controlled condition.
这一理念的最佳方法不是进行时间限制，而是预先制定在 CCS 发生偏差时应采取的步骤和措施方案。该方案不应说明要做什么，而应说明在将环境恢复到受控状态时要考虑什么。

Rationale
理由

Cleanroom facilities and operations differ. Therefore, it is impossible to prescribe time limits for reestablishing acceptable cleanroom conditions after a disruption for all facilities and operations. Companies should establish a clean-up period based on system qualification.
洁净室的设施和操作各不相同。因此，不可能规定所有设施和操作扰乱后恢复可接受的洁净室条件的时间限制。企业应根据系统确认的情况确定自净时间。

NOTE: EU Annex 1, Section 4.29, does state a guidance value of 20 minutes for cleanroom reestablishment of conditions, but says the time period should be determined under qualification and adhered to in operations.
注：EU Annex 1,第 4.29 节确实规定了洁净室重新建立条件的指导值为 20 分钟，但规定时间段应在确认活动中确定，并在操作中遵守。

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Topic K.1: Blow-Fill-Seal Process Design and Operation

主题 K.1：吹-灌-封工艺的设计与操作

Problem Statement
问题陈述

What are the unique environmental contamination control considerations for the Blow-Fill-Seal (BFS) process?
吹-灌-封（BFS）工艺有哪些独特的环境污染控制的注意事项?

Recommendation
建议

The environment in which the BFS machine is placed should be sufficient to protect the product- contact surfaces and product from environmental contaminants (typically Grade C). Open drains should not be present in the BFS filling cleanroom.
放置 BFS 设备的环境，应足以保护与产品接触的表面和产品免受环境污染（通常为 C 级）。BFS 灌装洁净室内不得有明沟。

The critical fill zone environment should be Grade A. This environment can be contained in an enclosed air shroud or barrier, providing that system is qualified and demonstrates a low risk of microbial intrusion.
关键灌装区的环境应为 A 级。该环境可包含在一个封闭的空气保护罩或屏障中，前提是该系统是合格的，并证明微生物入侵的风险很低。

It should not be necessary to have a Grade B transition area between the Grade A critical zone and the Grade C BFS machine area.
在 A 级关键区和 C 级 BFS 设备区之间不需要 B 级过渡区。

Qualification studies, including airflow visualization studies, should be performed to demonstrate that air from the environment does not flow from the surrounding fill room into the critical fill or exposed parison (transport) areas during operation and during interventions.
应进行确认研究，包括气流可视化研究，用以证明在操作和干预期间，环境中的空气不会从周围的环境流入关键填充区或暴露的型坯（运输）区。

The open parison transport environment should meet Grade A conditions and should be controlled and monitored to protect the interior and exterior of the container from contamination during transport. It may be necessary to utilize direct HEPA-filtered airflow over the parison cutting area.
开放式型坯运输环境应符合 A 级条件，并应加以控制和监测，以保护容器内部和外部在运输过程中不受污染。可能有必要在型坯切割区直接使用经过 HEPA 过滤的气流。

Machinery, equipment, and operations that can be placed outside of the filling room, or otherwise separated from the filling room by way of barriers or BFS line design, should be considered.
应考虑将机械、设备和操作放置于灌装室之外，或通过屏障或 BFS 生产线设计将其与灌装室隔开。

Cleanroom personnel performing interventions or otherwise entering the filling room should be gowned for

Grade A and Grade B. Any activities in the fill zone must use proper aseptic technique.
进行干预或以其他方式进入灌装室的洁净室工作人员应穿戴 A 级和 B 级防护服。灌装区的任何活动都必须使用适当的无菌技术。

Interventions should be minimized and limited to those performed outside of the enclosed air-shroud barrier systems and the critical fill and transport zones. A risk assessment should be used to determine which interventions are allowed and what steps should be taken to reduce the risk to product sterility as a result of interventions.
应尽量减少干预活动，并且其仅限于在封闭的气罩屏障系统以及关键的灌装和运输区域之外进行。应通过风险评估来确定允许采取哪些干预措施，以及应采取哪些措施来降低干预措施对产品无菌性造成的风险。

A risk-based approach to EM should be used to select monitoring locations based on areas where environmental contamination poses the greatest risk to product contamination, where EM data can best predict environmental-area control excursions, and where EM sampling does not pose an undue risk to product contamination or the monitoring system.
应采用基于风险的环境监测方法，根据环境污染对产品污染构成最大风险的区域、环境监测数据能够最好地预测环境区域控制偏差的区域、以及环境监测取样不会对产品污染或监测系统构成不当风险的区域来选择监测地点。

NOTE: For rotary or closed parison BFS machines, it may not be possible to take environmental samples adjacent to the filling nozzle due to the inclusion of the nozzle in the closed parison.
注：对于旋转式或封闭式 BFS 机器，由于喷嘴包含在封闭式型坯中，可能无法在灌装喷嘴附近采集环境样品。

Rationale
理由
A properly designed and operated BFS process may provide a relatively low risk for microbial ingress or contamination of product due to the high level of automation (no operators in the immediate filling area), minimal need for interventions, and short periods of container exposure to the controlled environment prior to filling and sealing.
由于高度自动化（在直接灌装区域没有操作人员）、干预需求最小以及灌装和密封前容器暴露在受控环境中的时间较短，使得设计和操作得当的 BFS 工艺可能会使微生物侵入或污染产品的风险相对较低。

Efforts to address potential risk of contamination, through BFS process design, should further mitigate the risk of contamination. Enclosed air-shroud or other barriers surrounding the critical fill zone creates a controlled environment around the fill system to reduce contamination risk.
通过 BFS 工艺设计来解决潜在的污染风险，应能进一步降低污染风险。关键灌装区周围的封闭式气罩或其他屏障可在填充系统周围创造一个受控环境，以降低污染风险。

Due to the design of the BFS process and equipment, it may be difficult to achieve a defined Grade A environment. It may not be possible to achieve correct differential pressures and an adjacent Grade B environment at the extrusion/parison cutting and transport areas. In addition, the parison cutting process may generate airborne particulates. As a result, equipment should be designed to minimize external particle generation and prevent introduction of particulates into containers. Qualification studies can help determine

a baseline of particles generated by the cutting process. This baseline can then be used to determine when excursions occur during production. Steps should be taken to examine the transport from the point at which the parison is cut and open to the point at which it enters the enclosed shroud area.
由于 BFS 工艺和设备的设计原因，可能很难达到确定的 A 级环境。在挤压/型坯切割和运输区域可能无法实现与邻近的 B 级环境之间正确的压差。此外，型坯切割过程可能会产生悬浮粒子。因此，设备的设计应尽量减少外部微粒的产生，并防止微粒进入容器。确认研究有助于确定切割过程中产生的微粒基线。然后可利用该基线确定生产过程中何时出现偏差。应采取措施检查型坯从切割和打开到进入封闭护罩区的运输过程。

Protection of the open parison during transport and filling should mitigate and control the risk of microbial contamination of the interior of the container and the exterior, given that the exterior will enter the critical fill zone area. Airflow volumes and velocity should be designed and balanced to minimize the risk of ingress of contamination, without creating excessive turbulence or unintentional cooling of the exposed parison, which could result in container formation and seal difficulties.
考虑到外部将进入关键灌装区，在运输和灌装过程中对开放型坯的保护应减少和控制容器内部和外部受到微生物污染的风险。气流量和气流速度的设计和平衡应能最大限度地降低污染物进入的风险，同时又不会造成过度紊流或无意中冷却暴露在外的型坯，从而导致容器成型和密封困难。

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Topic K.2: Plastic Resin Storage and Handling

主题 K.2：塑料树脂的储存和处理

Problem Statement
问题陈述
What are the unique container and resin control considerations for the BFS process?
对于 BFS 工艺，有哪些独特的容器和树脂控制注意事项?

Recommendation
建议
Resin identity and quality should be maintained through the company's approved supply-chain management system. Resin bioburden (including endotoxin) limits should be established, controlled, and monitored based on product requirements.
树脂的特性和质量应通过公司批准的供应链管理系统进行维护。应根据产品要求制定、控制和监测树脂生物负载（包括内毒素）限值。

Resin should be stored and dispensed from a controlled, non-classified area in a manner that prevents the introduction of extraneous contamination. Consideration should be given to temperature and humidity controls.
树脂的储存和分配应在受控的非洁净区域进行，以防止外来污染。应考虑温度和湿度控制。

Resin stored in large refillable containers (i.e., silos) should be monitored for moisture accumulation and bioburden. Such containers should be closed, periodically emptied, and cleaned or sanitized.
应监测储存在大型可再填充容器（即筒仓）中的树脂的水分积累和生物负载。此类容器应封闭，定期清空，并进行清洁或消毒。

Use of a resin-regrind mixture in container formation should be qualified to confirm that such regrind levels are acceptable. Acceptability should be based, at least, on the ability to maintain resin bioburden from the container and the seal of the container, and container integrity should be maintained throughout the shelf life of the product.
在容器成型中使用的树脂再研磨混合物应合格，以确认此类再研磨水平是可接受的。可接受性至少应基于保持容器中树脂生物负载和容器的密封性，并且在产品的整个保质期内应保持容器的完整性。

Procedures should be established for ensuring clearance and cleaning of current resin from the trans- port lines and extruder when the changeover of resin is required. Lot traceability of resin and resin- regrind mixture should be maintained.
应制定程序，确保在需要更换树脂时清除和清洁运输线和挤压机上的现有树脂。应保持树脂和树脂-再磨混合物的批次可追溯性。

Rationale
理由
The selection, use, and handling of resin are key components of the BFS process. Resin quality is important to

ensure the proper formation, sealing, stability, and overall performance of the containers and the control of bioburden; therefore, resin composition and identity should be maintained.
树脂的选择、使用和处理是 BFS 工艺的关键组成部分。树脂的质量对确保容器的正确成型、密封、稳定性和整体性能以及控制生物负载至关重要；因此，应保持树脂的成分和特性。

Proper handling and storage should reduce the risk of bioburden formation. Bioburden monitoring should provide additional assurance of resin quality. Steps should be taken to identify and address areas where excessive bioburden or other sources of contamination may be present in the process.
适当的处理和储存可降低形成生物负载的风险。生物负载监测可进一步确保树脂质量。应采取措施确定和解决过程中可能存在过量生物负载或其他污染源的区域。

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Topic K.3: Blow-Fill-Seal Process Simulation

主题 K.3：吹-灌-封工艺模拟

Problem Statement
问题陈述
What are the unique APS considerations for the BFS process?
对于 BFS 过程，APS 有哪些独特的考虑因素?

Recommendation
建议
APS for BFS should be conducted in the same manner as non-BFS aseptic processes.
用于 BFS 的 APS 应采用与非 BFS 无菌工艺相同的方式进行。

Rationale
理由
The level of automation, absence of inherent interventions, and visibility of media contamination in translucent, pigmented, or opaque plastic containers should be taken into consideration when designing the APS, as they would be in any aseptic filling process.
在设计 APS 时，应考虑自动化程度、无固有干预以及半透明、着色或不透明塑料 容器中介质污染的可视性，任何无菌灌装工艺都应如此。

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Topic L: Air Locks 主题 L：气锁

Problem Statement
问题陈述

Are separate air locks required for materials and for personnel to move into critical zones in order to prevent contamination?
为防止污染，材料和人员进入关键区域是否需要单独的气闸?

Recommendation
建议

Where possible, sterilized materials should be directly transferred into the critical zones after sterilization through double-door sterilizers or decontamination through other aseptic transfer devices. Where this is not performed, or cannot be performed, entry to these areas should be through separate air locks with an active air supply for (1) personnel and (2) equipment and materials.
在可能的情况下，灭菌后材料应在通过双扉灭菌器灭菌或通过其他无菌转移装置去污后直接转移到关键区域。如果不这样做或无法这样做，则应通过单独的气闸进入这些区域，并为（1）人员和（2）设备和材料提供主动供气。

Where it is not possible or feasible to physically separate the movement of personnel and materials or to have separate air locks, time-based separation of movement by procedure should be considered. Where an assessment aligned with the CCS indicates that the risk of contamination is high, however, separate rooms for personnel and material entering and leaving production areas should be used. The final area of a gowning room should be in at-rest (as-built) conditions of the same grade as the area into which this area leads.
在不可能或不可行对人员和材料的移动进行物理隔离或设置单独的气闸的情况下，应考虑按程序进行基于时间的移动隔离。然而，如果与 CCS 一致的评估表明污染风险很高，则应为进出生产区的人员和材料使用单独的房间。更衣室的最终区域应与该区域通往的区域处于同一静态（空态）等级。

The entrance into and exit from critical zones and Grade A and Grade B, including gowning rooms, should be through separate air locks or entrances. Gowning rooms for entrances into and exits from the controlled and graded areas should be designed with air locks and used to provide physical separation of the different stages of gowning and, thus, minimize microbial and particulate contamination of protective clothing and more highly controlled areas.
关键区、A 级和 B 级的出入口，包括更衣室，应通过单独的气闸或出入口。用于受控区和分级区出入口的更衣室应设计有气闸，用于对不同阶段的更衣进行物理隔离，从而最大限度地减少对防护服和高度控制区的微生物和微粒污染。

For equipment and materials, separate air locks for entrances and exits should be considered. If separate air locks are not possible, procedures should be in place to prevent entrances and exits without intermediate cleaning or sanitization.
对于设备和材料，应考虑为入口和出口设置单独的气锁。如果无法单独设置气锁，则应制定程序，防止进出口未经中间清洁或消毒。

Rationale

理由

The control of contamination as a result of personnel and material movement can be achieved through the segregation of entities, by means of the:

人员和材料移动造成的污染可通过实体隔离来控制，具体做法如下:

- Design of the process (e.g., double-door sterilizers)
  工艺设计（如双扉灭菌器）
- Use of separate air locks for personnel and materials
  人员和材料使用单独的气闸
- Unidirectional flow of personnel and materials
  人员和材料的单向流动
- Use of active air supply in the air locks
  在气闸中使用主动供气
- Use of interlocks and timed procedures for the opening of sequential airlock entrances
  使用联锁和定时程序打开顺序气闸入口

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Topic M: "At-Rest" and "In-Operation" Status

主题 M："静态"和"动态"

Problem Statement
问题陈述
Should we test or monitor cleanrooms for total particulates in "at-rest" conditions in addition to "in- operation" conditions?
除了 "动态 "条件外，我们是否还应该测试或监测洁净室在 "静态 "条件下的总粒子？

Recommendation
建议
For qualification and regular requalification, at-rest as well as in-operation test conditions should be used. Routine monitoring of at-rest conditions is not required as long as operational (total particulate) monitoring is in place.
对于确认和定期重新确认，应使用静态和动态测试条件。只要运行（总粒子）监测到位，就不需要对静态条件进行常规监测。

Consideration should be given to the analysis of total particulate monitoring of base levels for processes that inherently generate process-related particles, for example, containers closed by fusion or processes that otherwise generate product-related particles. These may include processes related to BFS, form-fill-seal, and powder filling.
对于本身就会产生与工艺有关的微粒的工艺，例如，通过熔合封闭的容器或以其它方式产生与产品有关的微粒的工艺，应考虑对基准水平的总粒子监测进行分析。这些工艺可能包括与 BFS、成型-灌装-密封和粉末灌装有关的工艺。

Rationale
理由
At-rest conditions are reflective of design and initial operation and should be periodically verified (i.e., during requalification) to ensure that no significant changes have occurred.
静态条件反映的是设计和初始操作，应定期进行验证（即在再确认期间），以确保没有发生重大变化。

At-rest monitoring may also be useful to establish baseline conditions that can be taken into consideration when setting in-process limits.
静态监测对于确定基准条件也很有用，在设定过程中的限值时可以将其考虑在内。

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Topic N: Sample Volume for Classification

主题 N：级别确定的采样体积

Problem Statement
问题陈述
What is the air volume, in relation to particles, to be sampled for classification purposes of cleanrooms?
为了对洁净室进行级别确定，与粒子有关的空气采样量是多少?

Recommendation
建议
The sample size described in the most current version of ISO 14644-1 should be used because this represents the current industry standard that is required by many regulators around the world.
应使用最新版本的 ISO 14644-1 中描述的样本量，因为这代表了世界各地许多监管机构要求的当前行业标准。

Rationale
理由
The ISO standard is based on scientific principles and industry expertise.
ISO 标准以科学原理和行业专业知识为基础。

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Topic O: ≥0.5 µm and ≥5 µm Total Particle Monitoring

主题 O: ≥0.5 µm 和 ≥5 µm 总颗粒的监测

Problem Statement
问题陈述

Should limits be applied for ≥5 µm particle monitoring for Grade A routine monitoring?[1]
是否应该为 A 级区日常监测设定≥5 µm 颗粒物限值?

Recommendation
建议

Routine monitoring for ≥5 µm within Grade A can provide useful information. However, due to the low concentration of particles and the possibility of false readings, the setting of limits may be misleading. The focus should be on the overall trend rather than individual numbers, based on the low accuracy of the measurement when counting particles ≥5 µm separately. The analysis of monitoring- result trends is more appropriate[1].
对 A 级区进行≥5 µm 的粒子进行常规监测，可以提供有用的信息。但是，由于颗粒浓度较低且可能出现读数错误，因此，限值的设定可能会产生误导。由于对≥5 µm 的颗粒进行单独计数时，测量精度较低，因此重点应放在整体趋势上，而不是单个数字上。对监测结果趋势进行分析更为合适。

Rationale
理由

ISO 14644-1:2015 states, "Sampling and statistical limitations for particles in low concentration make classification inappropriate…Sample collection limitations for both particles in low concentration and particles greater than 1 micrometer make classification of this particle size inappropriate, due to potential particle losses in the sampling system." Monitoring and reporting of particles ≥0.5 µm and≥5 µm should be adequate for evaluation of Grade A environments.[2] However, limits are not required for ≥5 µm particles for Grade A classification purposes.
ISO 14644-1:2015 规定："由于低浓度粒子的采样和统计限制，不宜对其进行分类……由于采样系统中潜在的粒子损失，低浓度粒子和大于 1 微米粒子的样品采集限制，不宜对这种粒径进行分类"。≥0.5 微米和≥5 微米的粒子监测和报告足以评估 A 级环境。

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[1] Quantification of ≥5 µm particle monitoring for Grade A zones, in addition to ≥0.5 µm particle monitoring, is currently required by some regulatory agencies, including in the EU.
目前，包括欧盟在内的一些监管机构要求对 A 级区域进行≥5µm 的粒子监测，以及≥0.5µm 的粒子监测。

[2] The same recommendation should apply to Grade B environments in nonoperational (as-built/at-rest) conditions (ISO Class 5).
同样的建议也适用于 B 级环境的非操作(空态/静止)条件(ISO Class 5)。

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II. Environmental Monitoring 环境监测

Topic A.1: Setting Alert Levels and Action Limits

主题 A.1:警戒限和行动限设置

Problem Statement
问题陈述

What are the recommended alert levels and action limits for aseptic processing areas?
无菌生产区的警戒限和行动限建议设置为多少?

Recommendation
建议

Each manufacturer should have a formal program that stipulates the EM monitoring alert and action limits and the methods used to determine them. However, any contamination in a Grade A area (and in Grade B areas surrounding the Grade A area) or on product-contact surfaces should be investigated and the impact on any product batches should be assessed prior to batch release.
每个生产商都应该有一个正式的方案，规定环境监测警戒限和行动限以及确定这些限值的方法。然而，A 级区域(以及 A 级区域周围的 B 级区域)或产品接触表面的任何污染都应该被调查，并且在批放行前应该评估其对任何产品批次的影响。

If new technologies are used for EM, the action limits for these methods should be at least comparable with the levels set for the established methods, with adjustments considered based on greater sensitivity of the new methods and agreed upon with regulators.
如果使用新技术进行环境监测，这些方法的行动限至少应该与既定方法的限值相当，根据新方法的更高敏感性考虑调整，并与监管机构商定，达成一致。

Alert levels should be based on historical data but should be lower than action limits so that it is possible to react before action limits are reached. *PDA Technical Report No. 13 (Revised 2022): Fundamentals of an Environmental Monitoring Program* suggests statistical methods to be used for determination of alert levels.
警戒限水平应该基于历史数据确定，但应该低于行动限，以便在达到行动限前作出反应。*PDA 技术报告第 13 号(2022 年修订版):《环境监测计划的基本原则》*建议使用统计方法来确定警戒限。

For new facilities, production lines, or other aseptic processing areas where historical data are not available, alert levels can be based on similar aseptic processing areas within the facility or at another facility or can be established by use of environmental data generated during validation studies. In any of these situations, EM data from the new area are generated and should eventually be used to reset the alert levels. Periodically thereafter, data should be reviewed and, if needed, alert levels may be adjusted (e.g., be made tighter or looser) based on the historical data. Caution should be used when limits are tightened to a level that approaches process capability. It is also noted that alert limits that are significantly higher than in trend data should also be avoided to ensure that a warning is triggered as soon as an abnormal situation occurs.
对于无法获得历史数据的新设施、生产线或其他无菌处理区域，可以根据设施内或其他设施内的类似无菌处理区域的环境监测数据，或通过验证研究生成的环境数据来确定警戒限。在上述任何情况下，都应该生成新区域的环境监测数据，并最终用来重置警戒限。此后定期审查数据，如果需要，可以根据历史数据调整警戒限水平(例如：变紧或变松)。 在将限值收紧到接近过程能力的水平时，应谨慎使用。还要注意，明显高于

趋势数据的警戒限值也应该避免，以确保一旦出现异常情况就会触发警告。

Rationale
理由

Some agencies have published recommended action limits for conventional monitoring methods; such limits should be considered levels because they are not product specifications and may be not adequate for newer testing methods.
一些机构已经公布了针对常规监测方法的建议行动限；这些限值应被视为水平，因为它们不是产品标准，可能不适合较新的检测方法。

In general, as a company designs its EM program, alert and action limits should be determined on the basis of an assessment of product contamination risk that takes into consideration product and process characteristics, process robustness, level of gowning, historical data, and other information relevant to product contamination risk.
总体而言，当一家公司设计其环境监测计划时，警戒限和行动限的确定应该基于对产品污染风险的评估，其中考虑了产品和过程特征、过程稳健性、防护装等级、历史数据和其他与产品污染风险相关的信息。

Not all situations require use of both alert and action limits; for example, it may not be possible to set alert levels for microorganisms in Grade A environments because any microorganisms present would require action.
并非所有情况都需要使用警戒限和行动限；例如：由于 A 级环境中存在的任何微生物都需要采取行动，因此可能无法为 A 级环境中的微生物设置警戒限值。

In general, EM trends are an important element in the evaluation of cleanroom performance. Due to the limited recovery capacity and the sampling nature of the methods, special attention should be given to the trends but without neglect of the single count result for the critical zones (Grade A or Grade B).
总的来说，环境监测趋势是评估洁净室性能的一个重要因素。由于方法的回收能力和取样性质的限制，应特别注意趋势，但不应忽视关键区域(A 级或 B 级)的单个计数结果。

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Topic B.1: Environmental Monitoring Alert and Action Limits

主题 B.1: 环境监测警戒限和行动限

Problem Statement
问题陈述

Should EM alert and action limits be considered specifications?
环境监测警戒限和行动限应该被视为标准吗?

Recommendation
建议

EM alert and action limits should not be considered specifications. However, any contamination in a Grade A or surrounding Grade B area or on product-contact surfaces should be investigated and the impact on any product batches should be assessed prior to batch release.
环境监测警戒限和行动限不应被视为标准。但，A 级或周围 B 级区域的任何污染，或者产品接触表面的污染都应该被调查，并且在批放行之前应该评估其对任何产品批次的影响。

Rationale
理由

Alert and action limits are used to monitor and control processes. Specifications relate to a direct measurement of product quality that is required to be met by an official monograph or filed application. Exceeding an alert or action limit does not produce an "out-of-specification" result. However, any contamination in a Grade A area or on product-contact surfaces may be indicative of a potential product contamination and should be investigated, and the impact on any product batches should be thoroughly assessed prior to batch release.
警戒限和行动限用于监控和控制过程。标准与官方各论或递交的申请要求符合的产品质量的直接测量相关。超过警戒限或行动限不会产生"超出标准"的结果。然而，A 级区域或产品接触表面上的任何污染可能表示潜在的产品污染，应该调查，并且在批放行之前，应该彻底评估其对任何产品批次的影响。

EM alert and action limits are established for the purpose of detecting potential adverse changes or drifts in a validated aseptic processing environment. These levels are typically derived from historical data and are set conservatively. As such, alert and action limits are occasionally exceeded. These situations provide early warning mechanisms that allow corrective actions to be taken before product quality is adversely affected. It is not appropriate to consider EM alert and action limits as extensions of product specifications because a cause-effect relationship does not automatically exist between EM level excursions and product contamination. This is evidenced by situations in which EM action limits are exceeded during zero-contamination-process simulations. Conversely, there are instances in which process simulation failures occur and no contamination is detected by EM.
环境监测警戒限和行动限的建立是为了检测洁净区环境的潜在不利变化或漂移。警戒限和行动限水平的设置通常来自于历史数据并进行严格地设置。因此，会偶发超过警戒限和行动限的情况。这些情况提供了预警机制，以便在产品质量受到不利影响之前及时采取纠正措施。 将环境监测警戒限和行动限视为产品标准的扩展是不合适的，因为环境监测水平超标和产品污染之间不会自动存在因果关系。这一点可以通过在零污染过程模拟中超过环境监测行动限的情况得到证明。相反，也有一些情况是过程模拟失败而环境监测没有

检测到污染。

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Topic C: Environmental Monitoring—Relationship to Batch Release

主题 C:环境监测与批放行的关系

Problem Statement
问题陈述

What is the relationship between EM data from Grade A and Grade B areas and batch release?
A 级和 B 级区域的环境监测数据与批放行之间的关系是什么?

Recommendation
建议

Microbiological and particulate EM data generated in Grade A and Grade B environments should be reviewed as part of the batch-release process. Microbiological and particulate EM data from lower- grade areas may also be considered. EM results that exceed established action limits in Grade A and Grade B areas should be investigated and reviewed, and the risk to product safety should be evaluated. A microbial count excursion of an established level, even in Grade A and Grade B zones, does not, by itself, mandate a batch rejection, provided that the investigation determines that there is no impact on product quality and safety. Excursions from action limits in lower-grade areas also require investigation, and this investigation may include impact on batch release.
A 级和 B 级环境中产生的微生物和粒子的环境监测数据应该作为批放行过程的一部分进行审查。批放行时也可以考虑较低等级区域的微生物和粒子的环境监测数据。超过 A 级和 B 级区域建立的行动限的环境监测结果应该被调查和审查，并且应该评估对产品安全性的风险。即使在 A 级和 B 级区域发生了微生物计数的偏差，也不一定要求拒绝批放行，前提是调查确定其对产品质量和安全性没有影响。较低洁净等级区域的行动限偏差也需要调查，调查需要包括对批放行的影响。

Rationale
理由

A carefully planned and executed EM program can provide a better understanding of the production environment. EM data are just one of many indicators used to evaluate an aseptic manufacturing process. Given the lack of accuracy and precision of a microbial count result, a single result alone may not be significant. However, any contamination in a Grade A and Grade B area or on product-contact surfaces should be investigated and the impact on any product batches should be assessed prior to batch release.
一个经过精心计划和执行的环境监测计划可以更好地了解生产环境。环境监测数据只是评估无菌生产过程的许多指标之一。鉴于微生物计数结果缺乏准确性和精确性，单个结果本身可能并不重要。然而，A 级和 B 级区域或产品接触表面上的任何污染都应该被调查,并且应在批次放行之前评估其对任何产品批次的影响。

Reaching or exceeding an environmental action limit does not necessarily indicate that the product is adversely affected. An action-level excursion should precipitate an investigation. The overall purpose of the investigation is to determine the source of contamination and establish, insofar as possible, the cause-effect relationship between the observed action-level microbial count and cause(s) of product impact of the excursion. The significance of an action-level excursion in EM and its impact on batch release is determined by a comprehensive investigation of all conditions that might impact the acceptability of the process and the batch (es) produced by that process.

达到或超过环境行动限不一定意味着产品受到不利影响。行动限超标应立即进行调查。调查的总体目的是确定污染源，并尽可能确定观察到的行动水平的微生物数量与超标产品影响之间的因果关系。对可能影响工艺接受能力的所有条件以及由该工艺生产的批次进行全面调查，以确定环境监测行动水平偏差的重要性及其对批次放行的影响。

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Topic D: Location, Frequency, and Duration of Viable and Total Particulate Monitoring

主题 D:活性粒子和总粒子监测的位置、频率和持续时间

Problem Statement
问题陈述
What should the location, frequency, and duration of viable and total-particulate EM be in classified cleanroom areas?
在洁净间区域，活性粒子和总粒子环境监测的位置、频率和持续时间应该是什么?

NOTE: The principles presented in this topic are applicable to decision-making and criteria selection for EM conducted in cleanroom areas, including Grade A filling areas and adjacent support areas. These principles are applicable to various processing technologies, including conventional fill rooms, RABS, blow-fill-seal, and isolators.
注：本主题中提出的原则适用于在洁净室区域（包括 A 级灌装区域和相邻辅助区域）进行的环境监测的决策和标准选择。这些原则适用于各种生产技术，包括传统灌装室、RABS 系统、吹-灌-封和隔离器。

Recommendation
建议
The location, frequency, and duration of EM should be based on scientific analysis and risk-based decision-making.
环境监测的位置、频率和持续时间应该基于科学分析、基于风险来制定。

- The monitoring program should be designed to provide evidence of control within the environment without compromising the safety of the product, regardless of the technology used to maintain the environment. The monitoring method should capture data in a manner that is effective in determining environmental control. Trend analysis should be performed to assess the capability of contamination-control measures.
  无论使用何种技术来维持环境，监测计划的设计应为不影响产品安全的情况下提供环境控制的证据。监测方法应该以有效的方式获取数据，来确定对环境进行控制。监测方法应进行趋势分析，以评估污染控制措施的能力。

- An understanding of the process and the inherent risk factors that can adversely affect product quality must exist. This includes selecting monitoring locations that will provide the best chance of detecting contamination in proximity to the product. The risk factors that should be considered include elements or conditions (including interventions) resulting from EM and the sterility of components and product-contact surfaces that may adversely affect the cleanroom environment to the extent that product quality is compromised.
  必须了解工艺流程以及可能对产品质量产生不利影响的固有风险因素。包括：为提供最佳机会检测产品附近的污染进行检测位置的选择。应考虑的风险因素还包括：环境监测的组件以及产品接触表面的无菌性所导致的可能对洁净室环境产生不利影响的元素或条件（包括干预），以至于影响

产品质量。

Companies should use risk assessment and analysis to determine which factors provide the needed information to make these decisions. Risk factors may include but are not necessarily limited to the frequency and duration of human activities in the monitored area; efficiency of the barrier and other control systems designed to protect the product; impact on the product of environment-borne contamination; additional controls and monitoring methods; historical data related to process failures; effectiveness of and risk associated with monitoring techniques; regulatory and organizational commitments; work (personnel; material; and process) flow; airflow and differential pressure; proximity to exposed components, products, or product-contact surfaces; and other factors that the company determines to have a potential impact.
公司应该利用风险评估和分析来确定哪些因素提供了做出这些决定所需的信息。风险因素可能包括但不局限于：监测区域人类活动的频率和持续时间；设计用于保护产品的屏障和其他控制系统的效率；环境污染对产品的影响；额外的控制和监测方法；与工艺故障相关的历史数据；监测技术的有效性和相关风险；监管和组织承诺；工作(人员、材料和工艺)流程；气流和差压；与暴露的组件、产品或产品接触表面的距离；以及公司确定的可能产生影响的其他因素。

NOTE: For more prescriptive criteria, practices, and requirements, see PDA TR-13.
注：关于更规范的标准、实践和要求,请参阅 PDA TR-13。

- The risk of performing the interventions associated with EM versus the benefit that EM information may provide should be considered. Location, frequency, and duration should be adequate to demonstrate control without the introduction of additional risk of microbial contamination by additional monitoring. Also, the use of EM methods that do not require human intervention or the use of media while still meeting the objectives should be considered. Duration is not a consideration for surface sampling; however, timing should be considered. Viable monitoring of sterilized product-contact surfaces should be performed only at the end of production. Not every product/component-contact surface may need to be monitored.
  应考虑执行环境监测相关的干预的风险与环境监测信息可能提供的益处。位置、频率和持续时间应该足以证明控制效果，而不会通过额外的监测增加微生物污染风险。此外，还应考虑使用不需要人为干预或使用培养基的环境监测方法，同时仍能达到目标。对于表面取样不考虑持续时间，但应考虑时间安排。只有在生产结束时才应对已灭菌的产品接触表面进行活性粒子监测。并非每一个产品/组件接触表面都需要监测。

Rationale
理由

Although the Grade A and Grade B aseptic processing area is not sterile, well-controlled Grade A and Grade B conditions are an important factor in ensuring product sterility. Although the correlation between the condition of cleanroom areas adjacent to the Grade A and Grade B area and the performance of the Grade A and Grade B area is not absolute, the monitoring of these adjacent classified areas is of scientific value and is recommended.
尽管 A 级和 B 级无菌加工区域不是无菌的，但良好控制的 A 级和 B 级条件对确保产品无菌至关重要。尽管相邻于 A 级和 B 级区域的洁净室区域的条件与 A 级和 B 级区域的性能之间的相关性不是绝对的，但对这些相邻的分级区域进行监测具有科学价值，因此推荐这样做。

Monitoring, although necessary to demonstrate control, also requires interventions that themselves present risk. Therefore, monitoring location, frequency, and duration must be carefully considered to optimize the benefit while the risk is managed. Excessive monitoring may add risk from human intervention with- out adding enough benefit to offset that additional risk. When EM interventions must occur, risk must be considered, and steps must be taken to minimize the effect on product. These steps may include the use of new technologies that do not require human intervention or the presence of nutrient media.
尽管监测对于证明洁净区域的控制是必要的，但也需要采取干预措施来防范风险。因此，必须仔细考虑监测位置、频率和持续时间，以达到优化获益，同时管理风险的目的。过度监测可能会增加人为干预的风险，而不会增加足够的收益来抵消额外的风险。当必须进行环境监测干预时，必须考虑风险，并采取措施，尽量减少对产品的影响。这些措施可能包括使用不需要人为干预或营养培养基的新技术。

Trend analysis is also recommended because of the inherent inaccuracy of any single microbiological EM result (i.e., colony-forming unit[1]). Although a single microbial result may not be indicative of a problem, an adverse trend is much more likely to be an early warning of a potential degradation or loss of control within the environment. Such adverse trends should be investigated to ensure that the cause is determined and control is retained.
建议进行趋势分析的另一个原因是，任何单个微生物环境监测结果(即菌落形成单位)都存在固有的不准确性。尽管单个微生物结果可能并不能说明问题，但不利的趋势更有可能预示环境中潜在的变差或失控的预警。应调查这种不利趋势，以确保查明原因并保持控制。

When available, technologies or methods that provide adequate scientific information and require minimal human activity in the Grade A and Grade B area should be considered.
当有条件的情况下，应考虑提供充分科学信息并以最小化人为活动的技术或方法，在 A 级和 B 级区域进行环境监测。

The level of human activity and the potential risk of media residue needed to perform surface monitoring in the Grade A and Grade B environment pose a risk of contamination of products, components, and product-contact surfaces. Therefore, this activity should be performed at the completion of the aseptic process.
在 A 级和 B 级环境中进行表面微生物监测所需的人类活动和介质残留存在潜在风险，会对产品、组件和产品接触表面造成污染。因此，这项工作应在无菌工艺结束后进行。

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[1] However, any single sample showing contamination in a Grade A and Grade B area or on product-contact surfaces should be investigated and the impact on any product batches assessed prior to batch release.
然而，在 A 级和 B 级区域或产品接触表面显示污染的任何单个样品都应进行调查，并在批放行前评估对任何产品批次的影响。

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Topic E: Investigation and Documentation of Environmental Monitoring Excursions

主题 E:环境监测超标的调查和记录

Problem Statement
问题陈述
How should EM excursions be investigated and documented?
环境监测超标应如何调查和记录?

Recommendation
建议
Elements to include in the investigation depend on the sample type where the action-level excursion occurred. Suggestions on which elements to include in the investigation can be found in PDA TR-13. The corrective and preventive actions must be documented and kept as good manufacturing process (GMP) documentation for investigations in relation to exceeding action limits. Additional details on investigation elements can be found in PDA *Technical Report No. 88: Microbial Data Deviation Investigations in the Pharmaceutical Industry.*
调查中应包括的要素取决于发生行动水平偏离的样本类型。关于调查应包含的要素，可参见 PDA TR-13。必须将纠正和预防措施连同超出行动限的调查过程进行记录，并作为 GMP 文件的一部分进行保存。关于调查要素的更多详细信息，可参见 *PDA 技术报告 第 88 号：制药行业的微生物数据偏差调查*。

Records should be maintained as part of the routine EM program, including results for samples exceeding action limits and include description of the deficiency, possible causes, action steps and their schedule for implementation, identification of persons responsible for relevant corrective action, and evaluation of effectiveness of action steps. Evaluation of trends of the sample location and adjacent room/area and microbial excursion identification results should be included and documented in the investigation.
记录应作为日常环境监测程序的一部分进行维护，包括超过行动限的样本结果，并包括缺陷描述、可能原因、行动步骤及其实施时间表、相关纠正措施的负责人以及纠正预防措施的有效性的评估。调查并记录的内容应包括：对样本位置和相邻房间/区域的趋势的评估，以及识别的微生物超标结果。

The risk for product safety must be evaluated for EM results exceeding action limits in Grade A and Grade B. The investigation should include product impact assessment and evaluate the risk to other products manufactured in the same time frame.
对于 A 级和 B 级区域，超过行动限的环境监测结果，必须评估产品安全性风险。调查应包括：产品影响评估，并评估对同一时期内生产的其他产品的风险。

Rationale
理由
EM is a critical element of the sterility assurance program and is one of the most important measures of control in clean areas. It provides meaningful information on the quality of the environment and should promptly identify potential routes of contamination, allowing for corrective action to prevent product contamination.

环境监测是无菌保证计划的关键要素,也是洁净区域控制的最重要措施之一。它提供有关环境质量的有意义的信息，并能及时发现潜在的污染途径，从而采取纠正措施防止产品污染。

The documentation is used for recording and demonstrating that the environment has been in control during production of products, and also that the impact on product quality has been evaluated. Furthermore, the documentation should be used for checking the effectiveness of the corrective and preventive actions taken by reviewing previous investigations for similar occurrences.
文件用于记录和证明在产品生产过程中对环境的控制，以及对产品质量影响的评估。 此外，通过审查以前对类似事件的调查文件来检查所采取的纠正和预防措施是否有效。

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Topic F: Rooms Classification/Zoning for Terminally Sterilized Solution Products

主题 F：最终灭菌溶液产品的房间分级/分区

Problem Statement
问题陈述
What is the appropriate cleanliness grade for areas used in the manufacturing of terminally sterilized liquid products?
用于最终灭菌液体产品的生产区域是什么洁净度等级？

Recommendation
建议
A Grade D environment or better is typically suitable for the control of environmental microbiological risks during compounding of a terminally sterilized product formulation as long as microbial ingress and growth risks at this stage of manufacturing are properly mitigated. A Grade C environment or better is typically suitable for the control of environmental microbiological risks during the filling of terminally sterilized liquid product formulations as long as microbial ingress and growth risks are properly mitigated at this stage of manufacture.
D 级背景或 D 级以上的环境，通常适用于控制最终灭菌产品处方配制过程的环境微生物风险，只要在处方配制阶段适当降低微生物污染和生长风险即可。C 级背景或 C 级以上背景的环境，通常适用于控制最终灭菌产品灌装过程的环境微生物风险，只要在灌装阶段适当降低微生物污染和生长风险即可。

Based on risk assessment and historical data, higher environmental classifications may be required for compounding and filling operations for terminally sterilized liquid products. The risks of microbial ingress originating from WFI and formulation ingredients should be addressed and mitigated through the use of initial microbiological risk assessment followed by ongoing microbiological testing to ensure that the microbiological content of raw materials is low and under a high state of control. The compounding and solution transmission system (mix tank to filter to filler piping system) should be a closed system (the compounding portion open to the environment only when actively adding ingredients), thereby minimizing the potential for ingress of microorganisms into the process stream during the compounding and filling processes. This system should also be regularly cleaned and sanitized as an additional microbial control.
根据风险评估和历史数据，对最终灭菌液体产品的配制和灌装操作可能需要更高的环境级别。应通过初步的微生物风险评估和持续的微生物监测来解决和降低注射用水和原辅料的微生物污染风险，以确保原材料的微生物含量低并处于高度受控状态。配制和溶液传输系统（从配液罐到过滤器再到灌装机管道系统）应是一个密闭系统（配制工序仅在投料时开口接触环境），从而最大限度地降低微生物在配料和灌装过程中进入工艺流的可能性。该系统还应定期清洗和消毒，作为额外的微生物控制措施。

Rationale
理由
Microbiological control of the manufacturing environment is essential to prevent risks to sterilization efficacy and endotoxin content in products.

生产环境的微生物控制是控制灭菌效果和产品中内毒素含量风险的关键。

The manufacturing process for terminally sterilized solution products typically consists of the following primary steps:
最终灭菌溶液产品的生产过程通常包括以下主要步骤：

1. Compounding of pharmaceutical ingredients in WFI to appropriate formulation requirements
   按照批准的处方要求在注射用水中配制药物原辅料
2. Filtration of solution (0.45 micron (µm) or better)
   溶液过滤（0.45 微米（µm）或更小）
3. Filling and sealing of solution into the container–closure system
   将溶液灌装到容器密封系统中并密封
4. Terminal sterilization (PNSU ≤10-6) of the solution and container–closure system
   溶液和容器密封系统的最终灭菌（PNSU ≤10-6）

The greatest microbiological risks for this process include:
该工艺最大的微生物风险包括：

1. Ingress of microorganisms into the process through WFI and other raw-material ingredients
   微生物通过注射用水和其他原辅料污染工艺
2. Ingress of microorganisms into the compounding system
   微生物污染配制系统
3. Growth of microorganisms in the aqueous formulation during the time between compounding and terminal sterilization
   从配制到最终灭菌期间处方配制溶液中微生物的生长
4. Ingress of microorganisms into the product during filling
   灌装过程中微生物污染产品
5. Ingress of microorganisms into the product from microorganisms resident on the container– closure system.
   容器-密封系统的微生物污染产品。

A Grade D environment is suitable for use for the compounding of terminally sterilized product formulations as long as microbiological risks are properly mitigated.
只要适当降低微生物风险，D 级背景就适用于最终灭菌产品的处方配制。

Many terminally sterilized solution formulations may potentially support the growth of microorganisms. However, the risk of uncontrolled microbial growth in aqueous solutions may be addressed through risk assessment and subsequent mitigation through refrigeration and/or by limiting the amount of elapsed time between compounding (when WFI and pharmaceutical ingredients initially combine) and the initiation of terminal sterilization.
许多最终灭菌溶液产品配方可能会支持微生物的生长。不过，水溶液中微生物不受控制生长的风险可以通过风险评估和控制措施来解决，控制措施为通过冷藏和/或规定配制（注射用水和原辅料开始混合）与开始最终灭菌之间的间隔时间。

A microbial retentive filter (0.45 µm or 0.2 µm) should be used prior to filling as a critical control point for each solution product to further mitigate upstream microbiological and particulate risks. An active filter-

integrity testing program must be in effect with passing integrity results a critical requirement for product release.
作为每个溶液产品的关键控制点，应在灌装前使用微生物截留过滤器（0.45 μm 或 0.2 μm）。以进一步降低上游微生物和微粒风险。过滤器完整性测试通过的结果是产品放行的关键要求。

Environmental microbiological risks pose the greatest risk to the product during the filling process. A Grade C environment is typically suitable for use as a control for environmental microbiological risks during the filling of terminally sterilized liquid products. Although there is a limited risk of ingress of microorganisms into the product or container from the environment, the effect of this contribution to the overall product bioburden should be considered and mitigated during the design of the terminal sterilization process and its associated delivery of physical and biological lethality to the product.

在灌装过程中，环境微生物风险是对产品构成最大的风险。C 级环境通常适用于在灌装最终灭菌液体产品期间作为环境微生物风险的控制。虽然微生物从环境进入产品或容器的风险有限，但在设计最终灭菌过程及其对产品的物理和生物致死作用时，应考虑并减轻微生物对产品整体生物负荷的影响。

Microbiological testing is to be employed with terminally sterilized solution products on an ongoing basis to evaluate the overall state of microbial control for the compounding to filling processes. Microbiological testing should be performed upstream of the microbial retentive filter and also on filled containers (presterilized product bioburden) immediately prior to exposure to the terminal sterilization process. A high state of microbial control can be demonstrated with historical bioburden data that shows low total counts and moist-heat-resistant spore counts. Action limits for product bioburden samples should be based on the sterilization cycle design approach utilized, including the physical and biological lethality delivered to the product.

应持续对最终灭菌溶产品进行微生物监测，以评估从配料到灌装过程的微生物控制整体情况。应对微生物截留过滤器的上游和最终灭菌工艺前的已灌装容器（灭菌前产品生物负载）进行微生物监测。如果历史生物负载数据显示总计数和耐湿热孢子计数较低，则可证明微生物控制处于较好水平。产品微生物负载样品的行动限应基于所使用的灭菌周期设计方法，包括传递给产品的物理和微生物致死率。

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Topic G: Cleaning and Disinfection Program for Grade A and Grade B Rooms

主题 G：A 级和 B 级房间的清洁和消毒程序

Problem Statement
问题陈述

How is a cleaning and disinfection program for a Grade A and Grade B room designed and qualified?
A 级和 B 级房间的清洁和消毒程序是如何设计和确认的?

Recommendation
建议

A disinfection program for Grade A and Grade B rooms should be designed to achieve an acceptable level of decontamination.
A 级和 B 级房间的消毒程序应达到可接受的净化水平。

The disinfection program should be designed based on a risk assessment that includes consideration of the following:
基于风险评估设计消毒计划，包括对以下方面的考虑：

- Cleaning of surfaces within the Grade A and Grade B rooms is a prerequisite for effective disinfection
  A 级和 B 级房间内的表面清洁是有效消毒的先决条件
- Disinfectant should be capable of achieving a 2log reduction for bacterial spores, 3 log reduction for vegetative/fungi to a spectrum of microbial flora (including site isolates) on representative surfaces
  消毒剂应能使代表性表面的微生物菌群（包括生产现场分离菌）的细菌孢子降低 2 个对数，营养体/真菌降低 3 个对数
- Disinfecting procedure should be capable of achieving not less than a 1 log reduction of bacterial spores or vegetative/fungi in a 1-5 minute contact time
  消毒程序应能在 1-5 分钟的接触时间内使细菌孢子或营养体/真菌的数量降低不少于 1 对数
- Chemical compatibility with the surfaces
  与表面的化学兼容性
- Effectiveness on different surfaces taking into account surface characteristics and necessary dwell time, wetting time, or contact time; this should be confirmed with in-house studies against actual surfaces using the actual application process in each facility and may be supplemented with reference to vendor literature.
  消毒程序在不同表面上的效果，需考虑表面特性和必要的停留时间、润湿时间或接触时间；这些应通过在每个设施表面使用实际消毒工艺的内部研究进行确认，并可参考供应商的文献资料进行补充。
- Feasibility and safety of application
  消毒程序的可行性和安全性
- Efficacy and reproducibility of the application procedure
  消毒程序的有效性和可重复性
- Potential disinfectant residues
  潜在的消毒剂残留
- Procedures defined in sufficient detail about the sequence and specific locations to be disinfected and

the detailed disinfection records (e.g., logbooks)
消毒程序规定详细地消毒顺序和特定消毒位置，以及详细的消毒记录（如记录本）。

Initial qualification typically includes the actual disinfection process, including the maximum time between disinfections, followed by more intensive environmental sampling.
首次确认通常包含实际消毒过程，包括两次消毒之间的最长间隔时间，然后是更密集的环境采样。

EM evaluates the efficacy of the disinfection program in an ongoing manner. The EM program should include trend analysis and periodic evaluation of changes in the environmental flora.
以持续环境监测的方式评估消毒程序的有效性。环境监测计划应包括趋势分析和对环境菌群变化的定期评估。

Rationale
理由

A disinfection program is dependent on a combination of the disinfecting chemicals selected, the physical surfaces to be disinfected, the cleaning of the physical surfaces, and the reproducibility of the disinfectant application process. The initial qualification of the disinfection process is designed to demonstrate confidence in the effectiveness of the process. Ongoing EM data demonstrates the effectiveness of the microbial contamination control system, which includes the disinfection program. The actual microorganisms found, the numbers, and the distribution within the facility compared to the trending history, indicate if the data are consistent with historical area performance or if there has been a shift in control.
消毒程序取决于选择的消毒化学品、需要消毒的物理表面、物理表面的清洁以及消毒剂使用过程的可重复性。消毒程序的初步确认目的是证明消毒程序有效性。持续的环境监测数据证明了微生物污染控制系统（包括消毒程序）的有效性。设施内实际发现的微生物、数量以及分布情况与历史趋势相比，表明数据是否与历史区域表现一致，或者控制是否发生变化。

Caution should be used when employing a vigorous wiping application during the validation of the effectiveness of the disinfectant agent because the wiping action may enhance the removal of contaminating entities.
在消毒剂的有效性验证时，用力擦拭的方法在使用时应小心，因为擦拭动作可能会促进污染实体的清除。

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Topic H: Identification of Environmental Isolates

主题 H：环境分离菌的鉴定

Problem Statement
问题陈述

What microbial identification strategy is appropriate for the EM of samples?
环境监测样品的微生物鉴定策略是什么？

Recommendation
建议

The characterization, identification, strain typing, potential source, and cause of microorganisms recovered from environmental and personnel monitoring are important parts of surveillance programs. The characterization and identification program selected by the laboratory should be defined in writing. This written description should specify the frequency of characterization and identification, the standard procedures for the methods used, and the consistency with regulatory expectations for identification. A characterization beyond the species level, a comparison of microorganism identification profiles, and the creation of a user-database may be useful in tracking and evaluating monitoring trends.
对从环境和人员监测中发现的微生物进行特征测定、鉴定、菌株分型、潜在来源和原因分析是监控计划的重要组成部分。实验室选择的特征测定和鉴定程序应有书面规定。书面描述应明确规定特征测定和鉴定的频率、所用方法的标准程序，以及与监管部门对鉴定的要求一致。除种级的特征测定以外，微生物鉴定图谱的比较以及用户数据库的创建可能有助于跟踪和评估监控趋势。

Table H.1 gives an example of a scheme for the extent of characterization that may be used for the recovered microbial isolates. The extent of characterization and rationale should be documented and should be determined on a case-by-case basis with consideration given to risk assessment, facility qualification, and appropriate trend analysis.
表 H.1 举例说明可对环境监测分离菌进行特征**测定**的范围。特征**测定**的范围和理由应记录，应根据具体情况确定，同时考虑风险评估、设施确认和适当的趋势分析。

Table H-1 Identification/Characterization Scheme
表 H-1 鉴定/特征测定方案

Extent of Identification/Characterization (Minimum Expectations) 鉴定/特征测定的范围（最低要求）	Isolate and Origin 分离菌和来源
Characterization (Gram stain reaction and morphology) only 仅特征测定（革兰氏染色反应和形态学）	Environmental monitoring of Grade C and D classification areas for alert-level excursions 对 C 级和 D 级分类区进行环境监测出现警戒限偏离
Identification to species level 鉴定到种级	Grade A and Grade B classification areas and alert and/or action-level isolates from excipient, finished product, environment, and water samples A 级和 B 级区域出现的以及来自辅料、成品、环境

	和水样中超出警戒限和/或行动限时的分离菌
Identification to strain level using such methods as strain typing, molecular fingerprinting (genotypic method), riboprinting 进行菌株分型、分子指纹（基因型方法）、核糖印迹等方法进行菌株鉴定	Significant product or process contamination failure (e.g., media fills or sterility tests) and significant adverse trends in environment and water monitoring 重大的产品或工艺污染失败（如模拟灌装或无菌检验）以及环境和水监测中出现重大的负面偏离趋势

NOTE: Care should be used in comparisons of results from different identification methods.
注：应注意比较不同鉴定方法的结果。

NOTE: As noted in EU Annex 1, "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."
注：如欧盟附录 1 所述，"还应考虑对 C 级和 D 级区域监测到的微生物进行鉴定（例如，超过行动限值或警戒水平的位置），或分离出可能证明失控、洁净度下降或可能难以控制的微生物（如微生物孢子和霉菌）进行鉴定，并保持足够的频率，以保持对这些区域典型菌变化的动态了解"。

For some types of processes and products, concern regarding specific organisms may determine the level of characterization and identification required. Initially, many isolates may be characterized and identified to establish a database of the microorganisms found in the area. Periodic identifications should be performed on routine monitoring to check for changes in predominant groups of microflora. A change in the microbial flora might signify a change in a system that should be investigated. Moreover, characterizations can be useful clues to the possible source of isolates. For example, *Staphylo-coccus* species are commonly found on skin, and *Pseudomonas species* are usually associated with water.
某些类型的工艺和产品，对特定微生物的关注可能会决定所需的特征测定和鉴定水平。最初，可对许多分离菌进行特征测定和鉴定，以建立该区域发现的微生物数据库。在日常监测中应定期进行鉴定，以检查主要微生物菌群的变化。微生物菌群的变化可能意味着系统发生了变化，应对这种情况进行调查。此外，特征测定为确定分离菌的可能来源提供有用的线索。例如，葡萄球菌通常存在于皮肤上，而假单胞菌通常与水有关。

Rationale
理由
The purpose of EM is to demonstrate whether the monitored environment is in a sustained state of control. Identification of EM isolates commensurate with risk is valuable toward understanding the sources and vectors for contamination.
环境监测的目的是证明受监测环境是否处于持续受控状态。基于风险的环境监测分离菌的鉴定对了解污染源和污染媒介是很有价值。

In cases where Grade C and Grade D areas are shown to be well in control, then action limit excursions will be infrequent. Therefore, it is advisable to periodically identify representative colonies of the recovered microorganisms to the species level, in order to have a full understanding of the flora in the Grade C and Grade D areas.

如果 C 级和 D 级区域能控制得很好，那么行动限值超标的情况就会很少发生。因此，为了全面了解 C 级和 D 级区域的菌群情况，最好定期对回收微生物的代表性菌落进行种级鉴定。

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Topic I: Growth-Promotion Testing of Environmental Monitoring Media

主题 I： 环境监测培养基的促生长试验

Problem Statement
问题陈述
What constitutes a scientifically appropriate program for routine growth promotion testing of EM media?
科学合适的环境监测培养基的常规促生长试验程序是什么？

Recommendation
建议
A quality management program for all incoming or in-house prepared media should be in place for evaluating media for its intended use and for its acceptance. Lots of media should be tested for their ability to reliably recover microorganisms. The growth-promotion test is one of the tests conducted by the microbiology laboratory that is used to achieve this. For growth-promotion testing of media used for EM, there should be a predefined list of test organisms. This list should include compendial organisms and may include environmental isolates if those isolates differ materially from compendial microorganisms. This list should represent a range of “representative” microorganisms that could be encountered in manufacturing environments (e.g., Gram-positive rod; Gram-positive coccus; filamentous mold and yeast; Gram-negative rod).
对所有外购或内部制备的培养基制定质量管理程序，以评估培养基的预期用途和验收情况。应测试各批次培养基培养微生物的能力。促生长试验是微生物实验室进行的测试之一，用于实现这一目标。在对用于环境监测的培养基进行促生长试验时，应预先确定一份测试微生物的清单。该清单应包括药典规定的微生物，如果环境监测分离菌与药典规定的微生物有重大差异，也可包括环境监测分离菌。该清单应代表生产环境中可能遇到的各种 "代表性 "微生物（如革兰氏阳性杆菌、革兰氏阳性球菌、丝状霉菌和酵母菌、革兰氏阴性杆菌）。

Growth-promotion testing may also demonstrate that the transportation route and different processing methods do not adversely impact the ability of the media to recover microorganisms.
促生长试验还可以证明，运输路线和不同的加工方法不会对培养基培养微生物的能力产生不利影响。

Skip-lot testing, in which not all of the lots are tested, might be justified based on consideration of risk elements, including but not limited to a robust supplier quality system, audit program, communication/notification policy, and experience with the vendor.
跳批记数抽样检验程序，即不对所有批次进行测试，可是基于风险因素的考虑，包括但不限于可靠的供应商质量体系、审核计划、沟通/通知政策以及与供应商的合作经验。

Rationale
理由
EM media should have demonstrated the capability to recover a range of potential microbial contaminants.
环境监测培养基应能培养各种潜在的微生物污染物。

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Topic J: Incubation Temperatures for Environmental Monitoring Samples

主题 J：环境监测样品的培养温度

Problem Statement
问题陈述
What incubation conditions are scientifically appropriate for EM samples?
环境监测样品的科学培养条件是什么?

Recommendation
建议
Mesophilic incubation conditions (a single temperature within the range of 20 °C to 35 °C ± 2.5 °C for three to seven days) are suitable for recovery of microorganisms from normal ambient-temperature manufacturing environments.
中温培养条件（20 °C ~35 °C ± 2.5 °C 范围内的单一温度，持续 3 至 7 天）适用于从室温条件的生产环境中监测微生物的培养。

Although detection of yeasts and molds can be improved by the use of specialized recovery media, a nonselective microbiological growth medium, such as casein soybean digest agar (or soybean casein digest agar (SCDA)), is suitable in most cases for the total aerobic flora.
虽然专门的培养基能提高酵母菌和霉菌的监测效果，但是非选择性微生物培养基，如酪蛋白大豆消化琼脂（或大豆酪蛋白消化琼脂(SCDA)）等在大多数情况下适用于需氧菌群的监测。

Assessment of environmental isolates and the incubation temperature regimen is recommended to confirm that the use of the nonselective media is sufficient to address the risk posed by any unique conditions in a particular cleanroom environment.
建议对环境分离菌和培养温度方案进行评估，以确认非选择性培养基的使用足以应对特定洁净室环境中任何特殊条件带来的风险。

Each manufacturer should select appropriate media and incubation regimens. The media used by various monitoring methods should be exposed and incubated according to the established EM program, and growth-promotion tests should be conducted using compendial standard organisms; these tests may include environmental isolates.
各生产商应选择适当的培养基和培养方案。各种监测方法所使用的培养基应按照已建立的环境监测 程序进行监测和培养，并应使用药典标准微生物进行促生长试验；这些试验可包括环境分离菌。

NOTE: Some studies have shown that recovery of yeast and mold may be hampered by incubation at higher temperatures (above 30 °C), but scientific consensus has not yet been established.
注：一些研究表明，在较高温度（30 °C 以上）下培养可能会影响酵母和霉菌的回收。但科学界尚未达成共识。

Rationale
理由

There is no universal set of incubation conditions that will reliably detect all types of environmental microorganisms that could be present from a given sampling site at a given point in time. It follows that the purpose of using a defined set of incubation conditions for detecting environmental isolates is to establish whether any microbial changes or shifts are occurring within the manufacturing environment.
没有一套通用的培养条件可以可靠地监测出在特定时间点从特定采样点可能存在的所有类型的环境微生物。因此，使用一套确定的培养条件来监测环境分离菌的目的是确定生产环境中是否发生了微生物变化或转移。

The use of a non-selective medium should be sufficient to achieve this objective. An assessment of environmental isolates should be performed to confirm that the use of the nonselective medium is sufficient to address the risk posed by any unique conditions in a particular cleanroom environment.
使用非选择性培养基应足以实现这一目标。应对环境分离菌进行评估，以确认使用非选择性培养基足以控制特定洁净室环境中任何特殊条件所带来的风险。

The recovery of environmental molds should be considered in the selection of the incubation temperature range and sequence of incubation temperatures, with a procedure and frequency based on risk assessment.
霉菌的监测在选择培养温度范围和培养温度顺序时，应考虑环境霉菌的生长情况，应基于风险评估确定程序和频率。

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III. Validation（Aseptic Process Simulation）

验证（无菌工艺模拟）

Topic A: Acceptance Criteria 主题 A：可接受标准

Problem Statement
问题陈述
What are the acceptance criteria for aseptic process simulations?
无菌工艺模拟的可接受标准是什么？

Recommendation
建议
The objective of APS is to produce zero contaminated units, irrespective of run size. Therefore, the target involving such simulations should be zero positive units.
无论批量大小如何，APS 的目标都是产生零污染的产品。因此，此类模拟的目标应该是零染菌。

Upon discovery of any positive units, an investigation that includes a comprehensive risk assessment should be performed to assess any potential root causes, implementation of corrective and preventive actions (CAPA), and respective documentation.
在发现任何阳性单位后，应进行包括全面风险评估在内的调查，以评估任何潜在的根本原因、纠正和预防措施（CAPA）的执行情况以及相关文件。

In addition to other qualification requirements, it may be advisable to include multiple process-simulation runs to verify the robustness[1] of the implemented corrective actions with consideration of the following:
除其他确认要求外，实施多次无菌工艺模拟运行，以确认所实施的纠正措施的稳健性，并考虑以下因素，是明智的：

- Potential for multiple root causes
  可能存在多个根本原因的可能性
- Unintended consequences inherently introduced by CAPAs that are otherwise not sufficiently challenged, or that may represent a departure from the original qualified state
  由 CAPAs 引入的内在的预料之外的后果，这些 CAPAs 要么没有充分进行挑战，要么代表了与初始确认状态的偏离。

Investigations that determine a definitive and readily identifiable root cause might provide grounds for a reduced number of repeat run(s). However, CAPAs should be put in place to avoid such issues and prevent deviations to studies and processes from reoccurring.
确定了明确且易于识别的根本原因的调查，可以为减少重复运行的次数提供理由。不过，应制定 CAPA 以避免出现此类问题，并防止重复出现研究偏差和工艺偏差。

In all cases, the execution of additional run(s) without the undertaking of a comprehensive risk-based investigation to identify and correct any potential root causes is not acceptable.
在任何情况下，在没有进行全面的风险调查以识别和纠正任何潜在的根本原因的情况下，执行额外的运行是不可接受的。

[1] 1 Robustness in this case is focused on the maintenance of sterility.
在这种情况下，稳健性的重点是保持无菌。

Rationale

理由

Process simulation contamination rates resulting in zero positive units should be achievable in well- designed and well-operated production lines.

在设计合理、运行良好的生产线上，工艺模拟污染率应该可以达到零阳性。

The APS provides additional, but not absolute, assurance of process control on a periodic basis. While part of the overall approach to process validation, process simulation is only one of the many tools or approaches designed to evaluate the processing steps for aseptic manufacture. The necessarily high degree of control and assurance for aseptic processes relies collectively on the qualification and validation of many systems, including product, equipment and component sterilization, personnel training and aseptic behavior, and environmental controls, and extends to facility design, inclusive of personnel, material, and equipment flows. Since these processes are linked to the overall control and assurance of asepsis, the occurrence of even a single contaminated unit in an APS may be indicative of an underlying issue in any one of these systems and should be viewed as a significant event.

APS 定期为工艺控制提供额外的保证，但不是绝对的。虽然是工艺验证的整体方法的一部分，但工艺模拟只是用于评估无菌生产加工步骤的众多工具或方法之一。无菌工艺所必须的高度控制和保证共同依赖于许多系统的确认和验证，包括产品，设备和部件的灭菌，人员培训和无菌行为以及环境控制，并延伸到厂房设计，包括人流，物流和设备流。由于这些流程与无菌操作的整体控制和保证息息相关，因此，即使是在 APS 中出现一个受污染的单元，也可能表明其中任何一个系统存在潜在问题，应将其视为重大事件。

Owing to the complexity and interdependencies of all aspects of aseptic processing and the limited diagnostic capability of the process simulation, a correlation between a specific event and a positive unit(s) is challenging. All positive units must be comprehensively investigated using the principles of quality risk management with a purpose of identifying the root cause(s), implementing CAPAs, and verification of the effectiveness and impact of those CAPAs, as applicable. This approach is required even in those circumstances where a definitive root cause is likely since the contamination may be due to multiple root causes or causal factors that should all be considered as part of the overall investigation conclusion.

由于无菌加工各方面的复杂性和相互依赖性，以及无菌工艺模拟诊断能力的有限性，要在特定事件和阳性单元之间建立关联具有挑战性。必须利用质量风险管理原则对所有阳性单元进行全面调查，目的是识别根本原因，实施 CAPAs，并酌情确认这些 CAPAs 的有效性和影响。即使在可能存在明确根本原因的情况下，也必须采用这种方法，因为污染可能是由多种根本原因或因果因素造成的，这些因素都应作为总体调查结论的一部分加以考虑。

In the event that a root cause cannot be established, the expectation is that all reasonable potential causal factors of the failure have been considered and steps have been taken to improve any and all identified issues arising from the investigation, including a comprehensive risk assessment. All deficiencies identified in the investigation and risk assessment should be addressed.

在无法确定根本原因的情况下，期望是已考虑到所有合理的潜在故障因果因素，并已采取措施改善调查中发现的所有问题，包括进行全面的风险评估。调查和风险评估中发现的所有缺陷都应得到解决。

NOTE: Based on the limitations of aseptic processing, a comprehensive investigation may conclude that the discovery of a single contaminated unit is not indicative of a failed process.

注：基于无菌加工的局限性，全面调查可能会得出这样的结论，即发现一个受污染的单元并不表明加工过程失败。

Recurring positive units in successive process simulations indicate a problem and should be investigated and resolved, even when the acceptance criteria are met for each individual simulation.
即使每次模拟都符合可接受标准，连续无菌工艺模拟过程中重复出现阳性单元也表明存在问题，应进行调查并加以解决。

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Topic B: Duration of Process Simulations versus Production

主题 B：无菌工艺模拟与生产的持续时间

Problem Statement
问题陈述

What is the appropriate duration of an APS run? How should APS address multiple shifts and campaign production runs?
APS 运行的持续时间应当是多长？APS 应如何处理多班生产和连续生产？

Recommendation
建议

The duration of the process simulation should be sufficient to adequately challenge the complete aseptic production process. Process simulation should focus on assessing the highest risk events that would be permitted during routine processing. Human interventions pose a risk to aseptic operation; therefore, consideration should be given to human variability in performance as well as the level of automation and barrier technology. If multiple personnel and shifts are involved, these should be ad- dressed in the risk evaluation and process simulation design. Batches filled over multiple days without intermediate sterilization, (i.e., campaign manufacturing) should be evaluated in the risk assessment and process simulation design. Please see the section "Isolation Technology" found in PDA *Technical Report No. 22: Process Simulation for Aseptically Filled Products* for additional information.
工艺模拟的持续时间应足以充分挑战完整的无菌生产工艺。工艺模拟应重点评估常规加工过程中允许发生的最高风险事件。人为干预会给无菌操作带来风险；因此，应考虑人为操作的可变性以及自动化和屏障技术的水平。如果涉及多个人员和多个班次，则应在风险评估和无菌工艺模拟设计中加以考虑。应在风险评估和无菌工艺模拟设计中对多天灌装而不进行中间消毒的批次（即连续生产）进行评估。更多信息请参阅 *PDA 第 22 号技术报告：无菌灌装产品的工艺模拟*中的 "隔离技术 "部分。

The duration of the process simulation should be risk-based and designed to simulate the conditions that provide the greater likelihood of uncovering process contamination (i.e., worst-case conditions). Each company must determine appropriate rationale and approaches applicable to their unique operations by means of a documented risk assessment and process simulation design.
无菌工艺模拟的持续时间应以风险为基础，旨在模拟更有可能发现过程污染的条件（即最差条件）。每家公司都必须通过记录在案的风险评估和工艺模拟设计来确定适用于其独特操作的适当理由和方法。

- The duration should be long enough to allow the simulation of the predetermined interventions, take into consideration the filling platform (i.e., closed isolators, RABS, automated, traditional/ conventional cleanroom, or manual filling operations), as well as other intrinsic characteristics of the containers and closure systems.
  持续时间应当足够长，使之能够模拟预定的干预，并考虑灌装平台（即，密闭式隔离器，RABS，自动的，传统的/常规的洁净室，或人工灌装操作），以及容器和密封件的其他内在特征。

- The duration of the process simulation should be long enough to fill the required number of units to ensure that the necessary activities and interventions are covered (even if longer than normal production).

无菌工艺模拟的持续时间应当足够长，灌装必要的数量，以确保涵盖必要的活动和干预（甚至是比常规生产时间长）。

- The risk assessment of the aseptic process should determine the number and frequency of interventions for each media fill, as well as any duration-related conditions or activities that should be included in the media fill. For lyophilization processes, consideration should be given to duration-related process variables, such as transport and handling of units and a representative chamber dwell time.
  无菌工艺模拟的风险评估应当确定每次模拟灌装的干预的数量和频次，而且任何与持续时间相关的条件或活动应当包含在模拟灌装中。对于冻干工艺，应当考虑与持续时间相关的工艺变量，例如转运和处理单元和代表性的腔室保持时间。

- Where there are no risk-based duration-related effects, and/or where longer duration does not add any scientific merit, it should not be necessary for a process simulation to be equal to or be longer than the maximum production duration.
  如果不存在基于风险的持续时间相关的影响，和/或较长持续时间不会增加更多的指标，无菌工艺模拟没有必要等同于或长于最大生产时间。

- Operations that extend over multiple days should also include an assessment of the maintenance of environmental conditions over the extended period of time.
  一些延续多天的操作也应当包括对延长的时间段的环境条件的维护的评估。

- Manual aseptic filling or closing processes are highly dependent on the operator's individual performance of the process. Therefore, it is recommended that full-duration media fills be used to qualify these processes.
  人工无菌灌装或密闭工艺高度依赖于操作人员的个人操作能力。因此，建议应当使用整个持续时间模拟灌装对这些工艺进行确认。

Rationale
理由

Contamination of an aseptic process is primarily a function of events rather than time. Therefore, the duration of the APS should be sufficient to assess the performance of those activities identified in a risk assessment as having the potential to introduce contamination. The maintenance of aseptic environ- mental conditions is best assessed through environmental system design and EM.
无菌工艺的污染主要是事件的函数而不是时间的函数。因此，APS 的持续时间应足以评估那些在风险评估中被确定为有可能引入污染的活动的执行。无菌环境条件的维护最好通过环境系统设计和环境监测评估。

Properly designed automation and barrier technology should reduce the frequency of, or risk associated with human interventions. These factors should be addressed in the risk assessment and process simulation design.
设计合理的自动化和屏障技术应能够减少人工干预的频次或相关风险。这些因素应在风险评估和无菌工艺模拟设计中加以考虑。

Good process design, including human-factor assessment, adherence to first-air principles, training, operations experience, monitoring, and ergonomics, and the scheduling of breaks and rest periods are better tools for controlling the performance of cleanroom operators, operations, and the potential effects of human

fatigue, than the passage of longer-duration media fills.
良好的工艺设计，包括人为因素评估、遵守初始气流原则、培训、操作经验、监控和人体工程学，以及休息时间的安排，是控制洁净室操作员工作情况、操作和人体疲劳潜在影响的更好工具，而不是通过更长时间的模拟灌装。

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Topic C: Incubation Temperatures 主题 C：培养温度

Problem Statement
问题陈述
What are suitable incubation temperatures for an APS?
APS 的合适培养温度是多少?

Recommendation
建议
Incubation conditions should be suitable for recovery of all potential microbial contamination. Generally, incubation conditions should be not less than 14 days at a designated temperature range between 20 °C and 35 °C. Each aseptic processing manufacturer should provide a scientific rationale for the selection of the incubation conditions including temperature. Literature data or growth promotion tests of environmental isolates may be used to support the selection of temperature range. Growth- promoting tests should be performed to confirm the suitability of the incubation temperatures and conditions. This may involve multiple temperatures. When multiple temperatures are used, the sequence and duration of temperature incubation should be justified.
培养条件应适合所有潜在微生物污染的回收。一般来说，培养条件应不少于 14 天，指定温度范围为 20 °C 至 35 °C。每个无菌加工生产商都应提供选择培养条件（包括温度）的科学依据。文献数据或环境分离物的促生长试验可用于支持温度范围的选择。应进行促生长试验，以确认培养温度和条件的适宜性。这可能涉及多个温度。使用多个温度时，应说明培养温度的顺序和持续时间。

Rationale
理由
Temperature conditions should be selected based on the knowledge of the characteristics of potential contaminants and process conditions. Most mesophilic environmental contaminants will grow at any temperature within the range of 20–35 °C spanning 14 days.
应根据对潜在污染物特性和工艺条件的了解来选择温度条件。大多数嗜常温环境污染物可在 20-35 °C 范围内的任何温度下培养 14 天会生长。

If incubation takes place at two different temperatures within the range of 20–35 °C, each temperature should include a minimum of seven days each.
如果在 20-35 °C 范围内的两个不同温度下进行培养，则每个温度下的培养时间至少应为 7 天。

The selection of incubation temperature should be qualified through growth promotion testing per- formed as part of design of the APS incubation procedure.
培养温度的选择应当通过促生长试验来确认，促生长试验作为 APS 培养规程设计的一部分来执行。

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Topic D: Incubation of Nonintegral and Rejected Units

主题 D：未密封和被剔除单元的培养

Problem Statement
问题陈述

Should nonintegral units and/or units that are otherwise procedurally deemed "rejected" units (during routine operations) be incubated and evaluated as part of the APS study?
未密封的单元和/或在程序上被视为 "被剔除 "的单元（在常规操作过程中）是否应作为 APS 研究的一部分进行培养和评估?

Recommendation
建议

As part of the APS design, every effort should be made to ensure that all integral[1] media-filled units are incubated. Procedurally defined nonintegral units, which are detected and discarded as part of the routine operation, should not be incubated (e.g., cracked vials or unsealed containers). Units that are rejected for other reasons (e.g., cosmetic or fill volume), which otherwise would not impact container– closure integrity and therefore sterility assurance, should be incubated and included in the study.
作为 APS 设计的一部分，应尽一切努力确保所有装有完整的已灌装培养基的单元都得到培养。程序上定义的未密封的培养基不应进行培养（如破裂的西林瓶或未密封的容器）。因其他原因（如外观或灌装量）而被剔除的单元，如果不会影响容器密封完整性，也就不会影响无菌保证，则应进行培养并纳入研究。

The exclusion of any units from incubation requires justification and documentation. It is important to include higher-risk conditions of the operation (e.g., first-filled units following setup operations or following significant interventions), if their inclusion does not introduce an artificially greater challenge to aseptic control than commercial operation (e.g., units removed by an automated process). Any exclusion of units should be based on the reproducibility of any exclusion in routine production. If written procedures and batch documentation adequately describe the removal of units not filled or sealed during an intervention, then those units do not need to be incubated. However, in no case should more units be removed, or a larger zone cleared, during a media-fill intervention than would be cleared during a production run.
将任何单元排除而不进行培养都需要说明理由并提供文件证明。重要的是将高风险的操作条件包括在内（如，安装操作后或重大干预后第一支灌装的单元），如果包括这些操作不会人为的引入相比于商业化生产（如，通过自动流程移除单元）的更大的无菌控制挑战。任何单元的排除都应当基于常规生产中任何排除的可重复性。如果书面规程和批文件充分描述了移除在干预过程中的未灌装的单元或未密封的单元，那么那些单元不需要进行培养。但是，在任何情况下，模拟灌装干预期间移除的单元，或清空的区域都不应当多于生产运行期间将会清空的区域。

Rationale
理由

The purpose of the APS is to evaluate those production steps that can have an effect on sterility and microbiological contamination of product. All process steps that may have an effect on sterility of the final

[1] Integral in this context means closed and sealed units.
在本文背景下，完整指的是密闭和密封的单元。

product should be included in the simulation. Any units filled during a media-fill, when considered representative of these process steps and therefore considered meaningful in support of the study, should be evaluated.
APS 的目的是评估那些可能对产品的无菌和微生物污染有影响的生产步骤。在模拟中应当涵盖所有可能对最终产品的无菌性有影响的所有工艺步骤。在模拟灌装中灌装的任何单元，当被认为能够代表这些工艺步骤时，并因此被认为对研究有意义，都应当进行评估。

By design, the APS study should include process conditions that provide the most challenge to the aseptic process and product sterility without introducing an artificially stringent challenge. An artificially stringent challenge, in the context of the media-fill, can be regarded as a challenge that is not considered representative of routine operations and, hence, not representative of product that could be commercially distributed. 通过设计，
APS 研究设计的工艺条件，应当对无菌工艺和产品无菌最具挑战性而不会引入人为的严格挑战。在无菌模拟灌装的背景下，人为的严格挑战可以看作是一种不能够代表日常操作的挑战，，因此，不能代表商业化分销的产品。

The incubation of nonintegral units will not provide any meaningful measure of the aseptic process, since these units do not represent either acceptable production practices or acceptable container-closure integrity. The removal of such nonintegral units is appropriate, as failure to do so may inaccurately represent the sterility control of normal operations. The incubation and post-incubation examination of nonintegral filled media-units would yield no significant scientific information. If the units were found to be nonsterile, by virtue of the nonintegral condition of the unit, there would be no means to ascertain that the contamination was the result of aseptic process failure rather than contamination entering the unit after leaving the fill room. If the unit was found to be sterile, then it would provide no reliable scientific information as to the ability to protect filled product from contamination in a nonintegral unit.
培养未密封的单元不会提供任何有意义的无菌工艺指标，因为这些单元既不代表可接受的生产实践，也不代表可接受的容器密闭密封完整性。移除此类未密封的单元是适当的，因为如果不这么做，可能无法准确代表常规操作的无菌控制。未密封的已灌装培养基的单元的培养和培养后的检查不会产生重要的科学信息。如果这些单元被发现是非无菌的，是由于单元的非密闭条件，可能没有方法弄清污染是无菌工艺失败导致的污染还是污染物在离开灌装间后进入未密封的单元。如果未密封的单元被发现是无菌的，那么不能提供可靠的科学信息证明未密封的单元有能力保护灌装的产品不被污染。

NOTE: Nonintegral units that are not discovered and removed prior to incubation, remain part of the study and, if found to be contaminated, are investigated as positives.
注：在培养之前未发现和未被移除的未密封的单元，仍然是研究的一部分，而且，如果发现被污染，作为阳性被调查。

For the APS, other defects that may routinely be rejected during commercial operations, via inspection processes or otherwise (e.g., cosmetic, particulate, and fill-volume defects), should be incubated and included in the evaluation and overall determination of contamination rate. The inclusion of these units is considered meaningful because the routine rejection of these vials is not related to consideration of sterility assurance. The inclusion of these units therefore provides insight into the ability of the process to maintain environmental control and sterility assurance.
对于 APS，在商业化操作中通过检查过程或其他（如，外观，颗粒，和灌装量缺陷）可能被例行剔除的其他

缺陷，应当被培养，并包括在污染率的评估和总体判定中。包括这些单元被认为是有意义的，因为日常剔除这些小瓶与无菌保证的考虑无关。因此，包括这些单元可为工艺保持环境控制和无菌保证的能力提供深入了解。

If a company does choose to incubate integral units that are normally rejected during interventions, the traceability of those units should be maintained in case those units exhibit post incubation contamination. In that case, an investigation of the contamination must be performed.
如果公司确实选择培养通常在干预过程中剔除的完整的单元，那么应当保持那些单元的可追溯性，以防那些单元表现出培养后的污染。在那种情况下，必须执行污染的调查。

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Topic E: Aseptic Process Simulation Reconciliation

主题 E：无菌工艺模拟数量的平衡

Problem Statement
问题陈述
What are the reconciliation/accountability requirements for APS?
APS 的数量平衡/衡算的要求是什么?

Recommendation
建议
The target for reconciliation of filled units should be 100%. Lacking 100% accountability is a deviation and must be investigated. The number of units rejected should be documented.
灌装单元的数量平衡的目标应当是 100%。缺少 100%的衡算即为偏差，而且必须经过调查。应当记录被剔除的单元的数量。

At a minimum, the following information should be documented:
至少应记录以下信息:

- Number of units filled
  已灌装的单元数量
- Number of units rejected and reasons for each rejection
  被剔除的单元数量和每个被剔除的原因
- Number of units incubated
  培养的单元数量
- Number of units inspected after incubation
  培养后检查的单元数量
- Number of units positive for microbial contamination
  微生物污染呈阳性的单元数量
- 100% reconciliation of incubated units is required.
  需要对被培养的单元进行 100% 的数量平衡。

Rationale
理由
Since any positive unit in a process simulation would exceed the acceptance criteria, 100% reconciliation/accountability of all incubated units should be the target.
由于无菌工艺模拟中的任何阳性单元都会超出可接受标准，因此应当将对所有被培养的单元进行 100%数量平衡/衡算记录作为目标。

Reconciliation of total processed units can be challenging based upon the variability and accuracy of counting systems, but efforts should be made to account for all units processed within normal production tolerances.
由于计数系统的可变性和准确性，对总的加工单元进行数量平衡可能具有挑战性，但应当努力考虑在正常生产公差范围内对加工的所有单元进行计数。

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Topic F: Inverting Units Prior to or During Incubation

主题 F：培养前或培养过程中的单位翻转

Problem Statement
问题陈述
Should APS units be inverted prior to or during some or all of the incubation period?
在某些或整个培养阶段之前或期间，是否应翻转 APS 单元?

Recommendation
建议
All filled units should be sufficiently manipulated prior to incubation to assure the contact of all sterile surfaces by the growth media. Such manipulations should be documented.
应当在培养前对所有已灌装培养基的单元进行充分操作，以确保培养基接触到所有无菌表面。此类操作应有文件记录。

Rationale
理由
A single inversion of test units is typically sufficient to allow the media to contact any microorganisms present on the upper inner surfaces of the container–closure system. Requiring inverted incubation should not be mandatory. If a method other than inversion (e.g., agitation or swirling) is used, then that method should be demonstrated to show that all interior product-contact surfaces are exposed to media. For certain complex containers or configurations, inversion alone may not be sufficient to ensure complete media contact. In these cases, special consideration should be given to selecting a dynamic and/or combination of manipulation methods.
一般来说，将试验装置翻转一次就足以让培养基接触到容器封闭系统上部内表面上的任何微生物。不应强制要求倒置培养。如果使用倒置以外的方法（如摇动或旋转），则应证明该方法可使所有与产品接触的内表面都接触到培养基。对于某些复杂的容器或配置，仅靠倒置可能不足以确保介质的完全接触。在这种情况下，应特别考虑选择动态和/或组合操作方法。

NOTE: The integrity of the container-closure system should be assessed in a separate evaluation.
注：容器密闭系统的完整性应当在单独的评估中进行评估。

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Topic G: Aerobic versus Anaerobic 主题 G：需氧与厌氧

Problem Statement
问题陈述
When should anaerobic APS fills be performed?
何时进行厌氧 APS 灌装?

Recommendation
建议
In rare circumstances, where true anaerobic conditions are achieved in production, an anaerobic media (e.g., fluid thioglycolate) should be considered, for example, where production is entirely in an anaerobic environment or where a confirmed, obligate anaerobe was isolated in a sterility test.
在极少数情况下，如果在生产中实现了真正的厌氧条件，则应考虑使用厌氧培养基(例如，硫乙醇酸盐流体培养基)，例如，如果生产完全在厌氧环境中进行，或者在无菌检查中分离出的已确认的专性厌氧菌。

Process simulation (i.e., media-filled) units should be processed and incubated under aerobic conditions using a general media such as SCDA. In those instances where inert gas headspace is used in production, that gas should be replaced with sterile air during media fills.
工艺模拟（即培养基灌装）装置应在有氧条件下使用 SCDA 等广谱培养基进行处理和培养。在生产中使用惰性气体顶空的情况下，应在培养基灌装过程中将惰性气体替换为无菌空气。

NOTE: Nitrogen overlay processes do not represent anaerobic conditions. If inert gas overlay is used in a process simulation, growth-promotion studies should be employed to ensure that inert-gas overlay does not inhibit aerobic or microaerophilic microbiological growth.
注：氮气覆盖工艺并不代表厌氧条件。如果在工艺模拟中使用惰性气体覆盖，则应进行促生长试验，以确保惰性气体覆盖不会抑制需氧或微需氧微生物的生长。

Rationale for Recommendation
建议的理由
The purpose of an APS is to assess the ability of the aseptic production process to prevent the introduction of microorganisms. Since that production occurs in aerobic environments, aerobic processes should be used for media fills. Any isolated microbial contamination that may be present is more likely to consist of aerobes and microaerophilic microorganisms than true anaerobes. Conducting an anaerobic media fill provides little or no significant scientific information, except possibly under the conditions noted in the Recommendation section.
APS 的目的是评估无菌生产过程防止微生物侵入的能力。由于无菌生产是在有氧环境中进行的，因此培养基灌装应采用有氧工艺。任何可能存在的分离污染的微生物都更有可能由需氧菌和微需氧微生物组成，而不是真正的厌氧菌。进行厌氧培养基灌装只能提供极少或根本无法提供重要的科学信息，除非是在建议部分所述的条件下。

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Topic H: Aseptic Process Simulation Boundaries

主题 H:无菌工艺模拟界限

Problem Statement
问题陈述
What are the boundaries for APS? Can the APS be performed in discrete segments?
APS 的界限是什么？APS 可以分段进行吗？

Recommendation
建议
The APS begins after the sterilization of materials and components and ends with the closure of the final container.
APS 在物料和部件灭菌后开始，并在最终容器密封时结束。

Any downstream aseptic connection of the sterile filter assembly or downstream aseptic manipulation, such as those associated with the performance of a pre-use post-sterilization integrity test (PUPSIT), represents an intervention, and it must be represented in the APS. The efficacy of the sterilizing filtration of the product should be demonstrated by a separate validation. The use of a different filter for sterilizing the media is acceptable.
无菌过滤器组件的任何下游无菌连接或下游无菌操作，例如与灭菌后使用前完整性测试(PUPSIT)的性能相关的操作，都代表一种干预，必须在 APS 中表示。产品灭菌过滤的功效应通过单独的验证来证明。使用不同的过滤器对培养基进行灭菌是可以接受的。

The primary objective is to simulate the routine production process (i.e., non-segmented) during the performance of an APS. Consequently, segmentation should be avoided if feasible. However, if justified and documented, then the APS might be performed as discrete segments. In this case, each segment should overlap the previous one and the following one. This approach should be described in a protocol that includes a rationale or risk assessment for adopting a segmented approach.
主要目标是在 APS 执行期间模拟常规生产过程(即非分段)。因此，如果可行的话，应该避免分段。但是，如果理由充分并有文件证明，则可以将 APS 分段执行。在这种情况下，每个分段都应该与前一个分段和后一个分段重叠。这种方法应在方案中加以说明，该方案应包括采用分段方法的理由或风险评估。

Rationale for Recommendation
建议的理由
An APS must start at the point where the aseptic process starts. The filter should not be considered part of the APS, as qualification of filter sterilization and filter-sterilizing capabilities are separate activities. The performance of PUPSIT presents a potential risk downstream of the filtration and, therefore, should be included in the APS.
APS 必须从无菌工艺的起点开始。过滤器不应被视为 APS 的一部分，因为过滤器灭菌和过滤器灭菌能力的确认是单独的活动。PUPSIT 的执行对过滤的下游有潜在的风险，因此，应该包括在 APS 中。

In some cases, it may be appropriate to perform an APS, for instance, where the overall segments cover all process steps (i.e., each segment should overlap the previous one and the following one, so that the media

passes through the contiguous/consecutive stages of the aseptic manufacturing process). For example, aseptic holding studies may be conducted separately from aseptic filling. This ensures all microbial ingress risks are encountered by the media as would normally be encountered by the product. The strategy, rationale, and acceptance criteria for this approach must be clear and identified in advance of execution.

在某些情况下，执行 APS 可能是合适的，例如，总体分段涵盖所有工艺步骤（即，每个分段应与前一个分段和后一个分段重叠，以便培养基通过无菌生产工艺的连接/连续阶段）。例如，无菌保持研究可与无菌灌装分开进行。这样可确保培养基遇到的所有微生物侵入风险与产品通常遇到的风险相同。该方法的策略、基本原理和可接受标准必须在执行之前明确并确定。

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Topic I: Fill Volume 主题 I：灌装体积

Problem Statement
问题陈述

What fill volume should be used for APS in order to assess potential contamination?
为了评估潜在的污染，APS 应该使用多大的灌装量?

Recommendation
建议

Fill volume should be sufficient to assess potential microbial contamination and to ensure complete contact with all sterile surfaces inside the container when inverted. The volume used should provide adequate headspace to support potential contaminant growth and enough volume should be present to visually determine growth. Where the headspace is found to be insufficient to support growth or the volume is found to be insufficient to detect contamination, adjustments to the headspace or the volume in the production scale container should be made.
灌装量应足以评估潜在的微生物污染，并确保倒置时与容器内所有无菌表面完全接触。所使用的体积应该提供足够的顶部空间以支持潜在的污染物生长，并且应该有足够的体积来目测生长。如果发现顶部空间不足以支持生长，或者发现容积不足以检测污染，则应调整产品容器的顶空或容积。

Rationale
理由

APS should simulate as closely as possible the actual production in order to capture any potential inherent risks or variables that could negatively impact the process (e.g., foaming, splash-up). The adequacy of headspace to support potential contaminant growth should be verified during growth-promotion studies. Where production-fill volumes are too small to be visually inspected for contaminant growth, fill volumes should be increased to the level where visual inspection is effective.
APS 应尽可能地模拟实际生产，以捕获任何潜在的固有风险或可能对工艺产生负面影响的变量(例如，起泡、飞溅)。在进行促进生长试验时，应确证顶部空间是否足以支持潜在污染物的生长。如果生产灌装量太小，无法目视检查污染物的增长，则灌装量应增加到目视检查有效的水平。

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Topic J: Interventions — Type and Frequency

主题 J:干预-类型和频率

Problem Statement
问题陈述
What types of interventions should be included in an APS and with what frequency?
APS 应包括哪些类型的干预?干预的频率是多少?

Recommendation
建议
The priority for an APS is designing the process to minimize the requirements for interventions and, that any interventions that are intended are designed to be as low a risk as possible. Any risks deemed requiring remediation activities to reduce their inherent risk should require those activities to be completed in order not to validate bad practices. The technique or method used to perform interventions in the aseptic fill should be captured or listed in a written procedure that may be enhanced by pictorial or videographic means. Aseptic-fill personnel should be trained in the performance of these interventions in such a way that the sterility of the product is not compromised. A list of approved qualified interventions should be maintained and should be reviewed on a regular basis to ensure the risk assessments remain current.
APS 的首要任务是设计流程，以最大限度地减少对干预的要求，并且预期的任何干预都设计尽可能降低的风险。任何被认为需要采取补救措施以降低其固有风险的风险，都应要求完成这些活动，而非验证不良做法。用于在无菌灌装中进行干预的技术或方法应被记录或列在书面程序中，该程序可通过图片或录像方式加强。无菌灌装人员应接受这些干预的培训，以确保产品的无菌性不受损害。经批准的合格干预清单应被维护，并应定期进行审查，以确保风险评估保持最新。

A risk-based assessment of interventions should be performed to plan for their inclusion in APS. This may include a grouping of interventions of a similar nature, provided that their complexity, risk, and execution are comparable. The rationale for any grouping should be documented.
应当执行基于风险评估的干预措施，以计划将其纳入 APS。这可能包括对性质相似的干预进行分组，前提是其复杂性、风险和执行情况具有可比性。任何分组的理由都应该记录下来。

The frequency of interventions to be included in the APS should be justified based on the risk assessment. The type of interventions and frequency in routine production may be identified from process design, production logs, records, and observation of the aseptic-filling process.
应根据风险评估结果合理确定 APS 中的干预频率。可通过工艺设计、生产日志、记录和对无菌灌装工艺的观察来确定常规生产中的干预类型和频率。

Interventions in routine manufacturing should be periodically compared to those interventions included in periodic process simulations to update the APS program.
应定期将常规生产中的干预与定期工艺模拟中的干预进行比较，以更新 APS 项目。

A new corrective intervention (e.g., one not included in the firm's APS program) performed during production must be evaluated as a deviation. The intervention may be determined acceptable if it is similar to a previously

simulated intervention and has been performed with proper aseptic technique. The evaluation of such an intervention may include an APS subsequent to the fill in which that intervention occurred. Evaluation of such a corrective intervention should be supported by a risk assessment. The assessment should conclude with either an acceptance or rejection of this intervention relative to the current and future manufacturing processes. If the new intervention is accepted, then it should be reviewed for inclusion into the list of identified interventions simulated during a scheduled APS.

在生产过程中进行的新的纠正性干预（如未列入公司 APS 项目的干预）必须作为偏差进行评估。如果干预与先前的模拟干预相似，并且采用了适当的无菌技术，则可以确定干预是可接受的。对此类干预的评估可以包括在产生干预的灌装之后的 APS。对这种纠正性干预的评估应以风险评估为依据。评估应以接受或拒绝与当前和未来生产工艺相关的干预作为结论。如果新的干预被接受，那么应该对其进行审查，，以便将其纳入已确定的模拟干预清单中。

Where the presence of operators increases the risk of contamination, worst-case conditions should be simulated by requiring each operator to participate in the process simulation for the maximum duration for which the operator may be present and operating in a cleanroom according to the procedure used in commercial manufacturing.

如果操作人员的存在会增加污染风险，则应模拟最差条件，要求每个操作人员参与工艺模拟，模拟其可能存在的最长时间，并根据商业制造中使用的程序在洁净室中进行操作。

Rationale

理由

Interventions should be designed and performed using proper aseptic techniques in order to minimize the risk of product contamination.

干预的设计和实施应采用适当的无菌技术，以尽量减少产品污染的风险。

The principle of an APS test is to assess the capability to perform a process (including interventions) under defined conditions to achieve units free from microbial contamination. The level of confidence that the same acceptable result (sterile production) can be achieved when performing the same process for actual (not simulated) production conditions is thereby supported. This confidence is supported by the firm's ability to monitor and control conditions during the APS test, and to verify the same/similar conditions every time the process is performed. The design of the aseptic process, training of aseptic-processing personnel, and use of aseptic technique in the performance of the intervention are essential. This simulation test must be performed periodically to reconfirm this capability.

APS 测试的原则是评估在规定条件下执行工艺（包括干预）以实现无微生物污染的单元的能力。因此，在实际（而非模拟）生产条件下执行相同的工艺时，可达到相同的可接受结果（无菌生产）的信心水平得到了支持。这种信心来自于企业在 APS 试验期间监测和控制条件的能力，并在每次执行过程时验证相同/类似的条件。无菌工艺的设计、无菌操作人员的培训以及在干预过程中无菌技术的使用都至关重要。这种模拟试验必须定期进行，以再次确认这种能力。

Including the presence of operators for the maximum permitted time during normal routine production in the simulation allows assessment of those operators' capability to work and behave properly in the cleanroom, despite the increased fatigue over time.

将操作员在正常的常规生产过程中的最大允许时间纳入模拟，可以评估这些操作员在洁净室中正常工作和行为的能力，尽管随着时间的推移疲劳程度会增加。

Similarly, within an APS test, the inclusion of certain activities (e.g., interventions) is directed at the demonstration of the capability to perform those activities and to achieve an acceptable result. It is not based on demonstration that the number of repetitions of these actions is directly connected to the capability to perform those actions. It should be understood that an APS in and of itself is not sufficient to qualify interventions. Qualified interventions should first undergo a risk assessment to understand the suitability of the intervention and, depending on the risk-level of the intervention, be confirmed by smoke studies prior to being simulated in an APS.

类似地，在 APS 测试中，包含某些活动(例如，干预)的目的是演示执行这些活动的能力并获得可接受的结果。它并不是基于重复这些动作的次数与完成这些动作的能力直接相关的证明。应该理解的是，APS 本身并不足以证明干预是合格的。合格的干预应首先进行风险评估，以了解干预的适用性，并根据干预的风险水平，在模拟 APS 之前通过烟雾试验进行确认。

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Topic K: Video Recording

主题 K:录像

Problem Statement
问题陈述
Should APS be video recorded and how long should recordings be kept?
APS 是否应录像?录像应保存多长时间?

Recommendation
建议
Video recording of APS is not a mandated requirement and should be optional based on the manufacturing organization's internal policies and procedures.
APS 的视频录制不是强制性要求，应根据生产组织的内部政策和程序选择。

Video recordings of process simulations, in addition to human observation, can be extremely useful, not only as a training tool but as an investigative tool in the evaluation of positive units and for the evaluation of aseptic training efficacy.
除人工观察外，工艺模拟的视频录像也非常有用，不仅可作为培训工具，还可作为评估阳性单位的调查工具和评估无菌培训效果。

If used as part of an investigation, the applicable sections of the video records should be retained as any other GMP documentation. The video record may then be referenced in any deviation raised. Each manufacturer should have a procedure that defines the purpose of the video record, how it is to be used, and its retention period.
如果视频记录被用作调查的一部分，则应与任何其他 GMP 文件一样保留。然后，视频记录可以在提出的任何偏差中引用。每个生产企业都应制定一套程序，规定视频记录的目的、使用方法和保存期限。

NOTE: The internal privacy policy of the company should be considered in the use of video recording of personnel operations.
注: 在使用录像记录人员操作时，应考虑到公司的内部隐私政策。

Rationale
理由
Video records allow for multiple reviews of the execution of the actual simulation process, which facilitates the investigation in case of product contamination. They can also be used for training new associates. There are inherent limitations to using video (e.g., limitation of camera angle view(s)) as the sole means to evaluate the aseptic process and these should be taken into consideration. Video recording equipment should be suitable for entry into an aseptic area, and its placement should not interfere with routine operations. Several countries have strict privacy and retention requirements related to video record retention; these should be taken into consideration when determining the timing for video record destruction.
通过视频记录，可以对实际模拟工艺的执行情况进行多次审查，这有助于在发生产品污染时进行调查。它们还可用于培训新员工。使用视频作为评估无菌工艺的唯一手段有其固有的局限性（如摄像机视角的局限性），

应将这些因素考虑在内。录像设备应适合进入无菌区域，其放置位置不应影响日常操作。一些国家对视频记录的保存有严格的隐私和保存要求；在确定销毁视频记录的时间时应考虑到这些要求。

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Topic L: Invalidated or Aborted Aseptic Process Simulation

主题 L: 无效或终止的无菌工艺模拟

Problem Statement
问题陈述

Under what conditions can an APS run be invalidated or aborted?
在什么情况下 APS 运行会失效或终止?

> **NOTE**: For purposes of this document, an invalidated run is one that was filled to completion and then invalidated. An aborted run is one that begins and is then stopped and not filled to completion.
> **注**：在本文件中，失效运行是指灌装完成后又失效的运行。终止的运行是指开始后被停止且未灌装完成的运行。

Recommendation
建议

Invalidation
失效

Invalidation of an APS run should be a rare occurrence and should be allowed only under circumstances in which the process is found to have been compromised by conditions external to the processes being simulated. An invalidated APS needs to be repeated.
APS 运行无效的情况应该很少发生，并且只有在发现模拟过程受到其外部条件影响的情况下才会允许。无效的 APS 需要重复。

The following may be reasons to invalidate an APS:
以下情况可能是导致 APS 失效的原因:

- Failure of growth promotion of media providing there are no positive units in the APS
  在 APS 中没有阳性单位的情况下，培养基的促生长失败
- Definitive evidence that the media used for the APS was not sterile (e.g., sterile filter integrity test failure).
  有确凿证据表明 APS 使用的培养基不是无菌的（如除菌过滤器完整性测试失败）。

Abortion
终止

An APS run may be aborted (discontinued) if conditions are present that would normally result in the stoppage of the production run. Any units that have been filled prior to discontinuation should be incubated, regardless of the number filled. These conditions should be described in a production procedure.
如果出现通常会导致停止生产的情况，则可终止（中断）APS 运行。终止前已灌装的任何单元，无论灌装数量多少，都应进行培养。这些情况应在生产程序中加以说明。

Documentation of the event(s) or conditions that caused discontinuation, and the disposition of any media-filled units from the APS should be collected, approved by the quality function, and maintained. Depending on the number of units ultimately filled, an additional APS may be necessary to supplement the aborted one.
应收集有关导致中止的事件或情况的文件，以及 APS 中任何培养基灌装单元的处置，经质量职能部门批准

后予以保留。根据最终灌装的单元数量，可能需要额外的 APS 来补充终止的 APS。

Rationale

理由

Media that does not support the growth of challenge organisms or is already contaminated at the start of the APS are not suitable for the detection of potential process contaminants.

不支持挑战生物生长或在 APS 开始时已被污染的培养基不适合用于检测潜在的工艺污染物。

Unexpected events that would pose an unacceptable risk to the aseptic process and would result in the stoppage and discontinuation of a production fill do not represent actual production conditions; therefore, they do not need to be simulated. Units filled with media prior to the stoppage of the run may, under normal production conditions, be considered acceptable product and therefore should be evaluated as part of the media fill for the APS run.

对无菌工艺构成不可接受的风险并导致停止和中断生产灌装的意外事件并不代表实际生产条件；因此，不需要进行模拟。在正常生产条件下，运行停止前已灌装培养基的单元可能被视为可接受的产品，因此应作为无菌操作运行的培养基灌装的一部分进行评估。

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Topic M: Number of Aseptic Process Simulation Tests Required

主题 M：无菌工艺模拟试验需要的次数

Problem Statement
问题陈述

How does a manufacturer determine the appropriate number of APS tests to be performed and when to perform them?
生产企业如何确定要执行的 APS 试验的适当次数及何时执行?

Recommendation
建议

For new processes or lines or when there have been changes to the processes, equipment, or manufacturing conditions, or when there have been extensive process disruptions, multiple APS runs should be performed.
对于新工艺或生产线，或当工艺、设备或生产条件发生变化时，或当出现巨大的工艺变化时，应执行多次 APS 运行。

NOTE: Most health authorities expect a minimum of three consecutive successful APS runs.
注：大多数卫生当局希望至少连续三次成功运行 APS。

The risk assessment may be used to determine if the changes represent an increased risk to the sterility of the product and therefore should result in multiple APS runs.
风险评估可用于确定这些变更是否增加了产品的无菌风险，因此应进行多次 APS 运行。

When companies are deciding on the minimum number of APS runs, they should take into consideration the following circumstances:
企业在决定 APS 实施的最少次数时，应考虑以下情况:

- In the absence of changes that could increase the risk of product contamination requalification, a single APS run, at a minimum, should be conducted semiannually.
  如果没有可能增加产品污染再确认风险的变更，应至少每半年进行一次 APS 运行。
- In circumstances where aseptic processing runs do not meet criteria, refer to recommendations in **Section III, Topic A**: Acceptance Criteria.
  如果无菌工艺运行不符合标准，请参阅第 III 部分主题 A：可接受标准中的建议。
- In circumstances where the novelty, duration, and/or complexity of a new routine process exceeds APS experience of the site and operators, a greater number of APS runs can be considered under risk assessment and management.
  如果新的常规工艺的新颖性、持续时间和/或复杂性超出了现场和操作人员的 APS 经验，则可在风险评估和管理下考虑进行更多的 APS 运行。
- If multiple processes and/or product configurations are being validated, a greater number of APS are required to adequately bracket the operations. The bracketing of processes should only occur when the processes share significant similarities and when the “worst case” can be simulated in both processes (e.g., a lyophilization line being bypassed to be liquid filling only).
  如果要验证多个工艺和/或产品配置，则需要更多的 APS，以充分涵盖这些操作。只有当工艺具有显著

的相似性，且两种工艺都能模拟 "最坏情况 "时（例如，忽略冻干生产线，仅进行液体灌装），才可对工艺使用括号法选择。

- Executing a media fill before shutdown should not prevent a full investigation and impact assessment of the batches manufactured, should the post-APS shutdown fail.
  在停机前执行培养基灌装不应妨碍对所生产批次进行全面调查和影响评估，以防停机后 APS 失败。

Rationale

理由

Multiple APS runs afford a better opportunity to uncover process variables that may adversely affect the performance of the aseptic process and therefore pose a higher risk of product contamination.
多次 APS 运行提供了更好的机会来发现可能对无菌工艺的性能产生不利影响的工艺变量，从而造成更高的产品污染风险。

Changes to the aseptic process should be evaluated to determine if they result in a greater risk of product contamination. Where these changes do result in increased risk, the process is considered as changed, and multiple process simulation runs should be considered to determine the potential impact these changes have on the process.
应对无菌工艺的变更进行评估，以确定这些变更是否会导致产品污染的风险增大。如果这些变更确实导致风险增加，则应认为工艺已发生变更，并应考虑进行多次工艺模拟运行，以确定这些变更对工艺的潜在影响。

Changes should be addressed using change control procedures, and a rationale for the number of runs must be documented. If there is a media-fill failure after a shutdown, prior batches must be investigated, unless the failure can be correlated to the changes that occurred during the shutdown.
变更应该使用变更控制程序来处理，并且必须记录运行次数的理由。如果在停机后出现培养基灌装失败，则必须对之前的批次进行调查，除非失败与停机期间发生的变更有关。

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Topic N: Infrequently Used Lines 主题 N：不常用的生产线

Problem Statement
问题陈述
How many APS runs should be performed for infrequently used lines or processing areas?
对于不经常使用的生产线或工艺区域，应执行多少次 APS 运行?

Recommendation
建议
If changes to the qualified aseptic process, equipment, personnel, or manufacturing area are not made, and if the equipment and area were maintained under demonstrated control during the time period that the line was not in use, then the procedures for semiannual requalification should be sufficient, with due consideration of ensuring that operator qualification requirements can be assured.
如果没有对合格的无菌工艺、设备、人员或生产区域进行变更，而且在生产线不使用期间，设备和区域保持在经证明的控制下，则半年一次的再确认程序应足够。同时应适当考虑确保操作人员的资格要求得到保证。

If changes were made or if the company is not able to demonstrate that control is maintained, then those changes or potential changes need to be addressed under the company's change-control procedure, the outcome of which may involve additional APS runs prior to recommencement of GMP production. Additional personnel retraining and requalification may also be necessary, as per organizational policies and procedures.
如果进行了变更或公司无法证明控制得到了维持，则需要根据公司的变更控制程序来处理这些变更或潜在变更，其结果可能涉及在重新开始 GMP 生产之前进行额外的 APS 运行。根据组织政策和程序，可能还需要进行额外的人员再培训和资格再确认。

Rationale
理由
If the aseptic process equipment and manufacturing area have been maintained under demonstrated control and there is no evidence of additional process variables, then the process can be considered as having remained in a qualified state. Since APS is not the sole or primary means to demonstrate ongoing aseptic process validation, when infrequent usage applies, companies should apply equal weight to ongoing process controls, results from EM, and maintenance of training. Therefore, the rationale for reinitiating GMP production for a line in a qualified state should be the same as for a line that is in more frequent use.
如果无菌工艺设备和生产区域一直保持在已证明的控制之下，而且没有证据表明出现了额外的工艺变量，那么就可以认为该工艺一直处于无菌状态。由于 APS 并非证明持续无菌工艺验证的唯一或主要手段，当不经常使用时 ，公司应同等重视持续的工艺控制、环境监测的结果和培训的维持。因此，对于处于合格状态的生产线，重新启动 GMP 生产的理由应与频繁使用的生产线相同。

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Topic O: Special Considerations for Aseptic Process Simulation in Isolators and Other Advanced Aseptic Processes

主题 O：隔离器和其他先进无菌工艺中无菌工艺模拟的特殊考虑因素

Problem Statement
问题陈述

What are the special considerations for APS in isolators and other advanced aseptic processes (e.g., closed-vial container filling)?
隔离器和其他先进无菌工艺（如封闭式容器灌装）中的 APS 有哪些特殊考虑?

Recommendation
建议

Following the same risk-based analysis and approach taken for APS of all current or advanced processing technologies is recommended.
建议对所有现有或先进的加工技术采用与 APS 相同的基于风险的分析和方法。

Rationale for Recommendation
建议的理由

The highest risk for contamination of an aseptic process is based upon the events that occur. The variability of the process (i.e., the level of human versus automated interventions) and the protection of the process (e.g., closed versus open, etc.) are risk factors that should also be addressed. Many isolator applications still involve a number of interventions that may represent a risk if performed poorly, and therefore it is not possible to generalize on the relative risk of a process in an isolator.
无菌工艺受污染的最高风险取决于发生的事件。工艺的多样性（即人工干预与自动干预的程度）和工艺的保护性（如封闭式与开放式等）也是需要考虑的风险因素。许多隔离器的应用仍然涉及一些干预措施，如果执行不力，可能会带来风险，因此不可能对隔离器中工艺的相对风险一概而论。

Isolators and closed-vial filling systems afford isolation of the aseptic process from microbiological contamination risks (e.g., operators and surrounding room environment) throughout processing. For such closed systems, robust design of the processing equipment and minimized manual manipulations in the manufacturing process might justify simulation of a lower number of interventions (e.g., shift changes) based on a comprehensive risk analysis.
隔离器和封闭式灌装系统可使无菌工艺在整个加工过程中与微生物污染风险（如操作人员和周围房间环境）隔离。对于此类封闭系统，加工设备的可靠设计和生产过程中人工操作的最小化可能会证明，根据全面的风险分析，模拟干预（如换班）的次数较少是合理的。

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Topic P: Hold Times for Sterile Bulk

主题 P：无菌原液的保持时间

Problem Statement
问题陈述

Should maximum hold times for sterile bulk be included in the APS for aseptic filling?
无菌灌装的 APS 中是否应包括无菌原液的最长保持时间?

Recommendation
建议

Maximum hold times may be included in the APS; however, the APS should not be used as the primary means to validate or qualify the maximum hold time for sterile bulk product/material. Nor should the APS be used to establish maximum production hold times.
APS 中可包括最长保持时间；但 APS 不应作为验证或确认无菌原液产品/材料最长保持时间的主要手段。也不应使用 APS 来确定最大生产保持时间。

The maximum hold time should be based on:
最长保持时间应基于:

- Production output requirements
  生产产量要求
- Stability of material/product and conditions required during the holding period
  材料/产品的稳定性和保留期间所需的条件
- Ability of the container, assemblies, and procedure to maintain the sterility of bulk material/product, as assessed in the CCS
  容器、组件和程序保持原液/产品无菌的能力，如 CCS 所评估的那样

Maintenance of the sterility of material/product should be qualified as part of a separate sterile hold study that includes an evaluation of the design of the holding vessels, assemblies, and procedures to maintain aseptic conditions for that period. The qualification should include an evaluation of the integrity of the holding container and assembly, and it may comprise studies that include holding sterilized media for the maximum hold time and then evaluating that media for microbial growth.
材料/产品无菌状态的保持应作为单独的无菌保持研究的一部分进行确认，其中包括对保持容器、组件和程序的设计进行评估，以便在此期间保持无菌状态。确认应包括对保持容器和组件完整性的评估，还可包括对灭菌培养基进行最长保持时间的研究，然后评估培养基的微生物生长情况。

If a single-use-system (SUS) container is used, separate container–closure integrity studies should be performed that demonstrate the ability of the SUS to maintain integrity over the maximum hold time. Containers, assemblies, and procedures used for holding sterilized materials should be qualified initially and on a periodic frequency as determined through a risk-based assessment and CCS.
如果使用一次性使用系统（SUS）容器，则应进行单独的容器密封系统完整性研究，以证明一次性使用系统在最长保持时间内保持完整性的能力。用于盛放灭菌材料的容器、组件和程序应进行初始确认，并通过基于风险的评估和 CCS 定期进行确认。

Once qualified, the maximum holding time should be considered in the design and performance of the APS. The hold time conditions assessed to be impacted by duration should be used as the rationale for determining the hold time required to be simulated in the APS study.
最长保持时间一经确定，就应在 APS 的设计和执行中加以考虑。在确定 APS 研究中需要模拟的保持时间时，应将评估出的受持续时间影响的保持时间条件作为依据。

Rationale
理由

Sterilized material/product must be held under conditions that maintain its sterility for the period of time prior to sealing.
灭菌材料/产品必须在密封前的一段时间内保持无菌状态。

Any bulk that is held as sterile bulk for an extended period of time should be held under conditions that are demonstrated to be:
任何作为无菌原液长期保存的原液，其保存条件应证明是：

- Compatible with product stability
  与产品稳定性兼容
- Able to maintain sterility
  能够保持无菌

This also further supports the container–closure integrity of the holding unit.
这也进一步确保储存单元的容器密封完整性。

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IV. Personnel 人员

Topic A: Glove Monitoring 主题 A：手套监测

Problem Statement
问题陈述

When and under what conditions should single-use operator gloves[1] be monitored or changed?
一次性使用操作手套[1]应在何时和何种情况下进行监测或更换?

Recommendation
建议

The monitoring and changing of sterilized, single-use gloves should be based on the specific process and on the evaluation of the risk to product, product components, and product-contact surfaces.
无菌一次性手套的监测和更换应基于特定的流程以及对产品、产品组件和产品接触表面的风险评估。

There are several situations where monitoring (microbiological sampling) should be conducted:
在以下几种情况下应进行监测（微生物采样）:

- After an intervention where inappropriate contact with product-contact surfaces may have occurred, such as a failure to adhere to first-air requirements or contact with surfaces instead of using an approved tool or device
  在进行干预后，可能发生了与产品接触表面的不当接触，例如未遵守首过新风（初始气流）要求，或未使用经批准的工具或装置而接触了表面。
- After critical interventions, for example after assembly of filling parts and line, open door intervention in RABS, and conventional fill line interventions.
  在关键干预之后，例如在灌装部件和灌装线组装之后，RABS 中的开门干预，以及常规灌装线干预之后。
- Periodically, as defined by internal procedures (at minimum upon every exit from the critical zone or the aseptic area).
  根据内部程序的规定定期进行（至少在每次离开临界区域或无菌区域时进行）。
- As deemed necessary based upon a specific process risk.
  根据具体工艺风险认为有必要时。

Monitoring of gloves should not occur immediately after sanitization, glove disinfection, and surface disinfection, because of the interference of disinfecting agent with the recovery of microorganisms.
在消毒、手套消毒和表面消毒后，不应立即对手套进行监测，因为消毒剂会干扰微生物的恢复。

Sterile gloves should be changed:
应更换无菌手套:

- When there are indications of tears, rips, or gaps.
  有撕裂、破裂或缝隙迹象时。

NOTE: Torn and ripped gloves during cleanroom operations should be recorded in the batch record; it may require a quality notification for product impact assessment if the damage occurred during critical manual operations.

[1] Isolator/RABS gloves are not within the scope of this topic.
隔离器/RABS 手套不在本主题范围内。

注：洁净室操作过程中撕裂的手套应记录在批记录中；如果损坏发生在关键的手工操作过程中，可能需要质量通知以进行产品影响评估。

- After an intervention or contact that may compromise the cleanliness of a glove and sanitization might not return the glove to the proper conditions
  在进行干预或接触后，手套的洁净度可能会受到影响，而消毒可能无法使手套恢复到适当的状态
- After all finger-impression plating
  在所有指压平板采样之后
- As deemed necessary based upon a specific process risk
  根据具体工艺风险认为有必要时

Care should be taken when changing out gloves to ensure that required monitoring is occurring after use and before the change out.
更换手套时应注意确保在使用后和更换前进行必要的监测。

Rationale
理由

The primary source of microbial contamination of aseptic processing areas is personnel. Sterile gloves are used to prevent the transfer of contamination.
人员是无菌操作区域微生物污染的主要来源。使用无菌手套是为了防止污染的转移。

Glove-changing and sanitization are key components of the contamination-control program. The purpose of monitoring is to assess the condition of the gloves after use.
手套更换和消毒是污染控制计划的关键组成部分。监测的目的是评估手套使用后的状况。

Sanitization of gloves directly before monitoring may compromise the integrity of this test by inhibiting microorganisms that may have been present. Therefore, procedures should specify the acceptable timing to allow a meaningful evaluation of glove contamination.
在监测前直接对手套进行消毒可能会抑制可能存在的微生物，从而影响检测的完整性。因此，程序应规定可接受的时间，以便对手套污染进行有意义的评估。

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Topic B: Aseptic Personnel Qualification Program

主题 B：无菌人员资格确认程序

Problem Statement
问题陈述

What is the process to qualify personnel to work in or access the aseptic processing area (Grade A and Grade B area)?
对在无菌操作区（A 级和 B 级区）工作或进入无菌操作区的人员进行资格审查的程序是什么？

Recommendation
建议

Companies should not rely solely on personnel meeting the Aseptic Personnel Qualification Program criteria or place an overreliance on the results of the APS to provide confidence on the efficacy of the aseptic process control strategy. Instead, companies should take steps to ensure that aseptic processes are designed to provide conditions that assist and permit personnel to perform aseptic manufacturing activities proficiently and that this demonstrated proficiency is maintained continuously. Hence, all relevant personnel should receive regular training and assessments.
公司不应仅仅依靠符合无菌人员资格确认程序标准的人员，也不应过分依赖 APS 的结果来保证无菌工艺控制策略的有效性。相反，公司应采取措施，确保无菌工艺的设计能够提供有助于并允许人员熟练执行无菌生产活动的条件，并持续保持这种已证明的熟练程度。因此，所有相关人员都应定期接受培训和评估。

The Aseptic Personnel Qualification Program should confirm that aseptic processing personnel have acquired general knowledge in background topics that are relevant to their job function and demonstrated their ability to reliably perform aseptic processing activities relevant to their job function in a specified manner that is designed to prevent microbiological contamination of product.
无菌操作人员资格确认程序应确认无菌操作人员已掌握与其工作职能相关的背景知识，并证明他们有能力以特定方式可靠地执行与其工作职能相关的无菌操作活动，以防止产品受到微生物污染。

The following is an example of a phased approach to personnel qualification that allows for operator participation in routine aseptic processing activities based on level of risk and required level of supervision. It does not necessarily establish different categories of operators, but rather describes the activities and criteria that would allow operators to progress through the phases of qualification towards a fully qualified status.
下面举例说明分阶段进行人员资格确认的方法，这种方法允许操作人员根据风险等级和所要求的监管水平参与常规无菌操作活动。它并不一定规定操作人员的不同类别，而是描述了允许操作人员通过各阶段的资格确认达到完全合格状态的活动和标准。

Aseptic Personnel Qualification Program
无菌人员资格确认程序

The Aseptic Personnel Qualification Program should be risk-based and comprise a demonstration of proficiency, degrees of supervision, and specified activities personnel are allowed to perform that are commensurate with the level of qualification achieved. It should allow for personnel to advance from lower-risk activities to higher-risk activities once they have met the qualification criteria of each level. The need for

direct supervision should be commensurate with these levels, with more direct supervision required initially and less supervision required as the personnel progress through the levels of qualification. More complex interventions and interventions assessed to have higher levels of risk should be performed by personnel with higher levels of skill and experience.
无菌操作人员资格确认程序应以风险为基础，包括熟练程度的证明、监督程度以及允许人员从事的与所达到的资格确认级别相称的特定活动。一旦人员达到每个级别的资格确认标准，该程序应允许他们从风险较低的活动晋升到风险较高的活动。对直接监督的需求应与这些等级相称，最初需要更多的直接监督，随着人员资格确认等级的提高，所需的监督会减少。更复杂的干预措施和被评估为具有更高风险的干预措施应由具有更高技能和经验的人员执行。

A phased approach should allow personnel to participate in defined activities based on meeting the criteria for that phase of qualification. It should include the allowable activities permitted based on meeting training and qualification requirements, and the level of supervision of personnel associated with the completion of levels of qualification.
分阶段方法应允许人员在达到该阶段资格确认标准的基础上参加规定的活动。它应包括在满足培训和资格确认要求的基础上允许开展的活动，以及与完成资格确认水平相关的人员监督水平。

Qualification Prerequisites
资格确认先决条件
The Aseptic Personnel Qualification Program should specify the prerequisite criteria for qualification acceptance, which should incorporate the successful completion of:
无菌操作人员资格确认程序应规定资格验收的先决条件，其中应包括成功完成以下培训：

1. Basic GMP training
   基础 GMP 培训
2. Aseptic gowning procedure training, followed by a proficiency-based assessment that demonstrates competency, leading to gowning qualification or certification
   无菌穿衣程序培训，然后进行能力评估，以证明胜任能力，从而获得穿衣资格确认或认证
3. Aseptic technique and cleanroom behavior training
   无菌技术和洁净室行为规范培训
4. Process understanding
   了解流程
5. Awareness of the impact of their performance and relevant hygiene on product quality and patient safety
   认识到自己的表现和相关卫生条件对产品质量和患者安全的影响
6. Basic applied microbiology and contamination-control training
   基本应用微生物学和污染控制培训
7. Specific job functions, intervention procedures and practical training, with consideration of participation in, or review of, airflow visualization studies to reinforce effect and understanding of first-air principles and the techniques employed to prevent first-air breaches, where relevant
   具体的工作职能、干预程序和实际培训，考虑参与或审查气流可视化研究，以加强效果和对初始气流原则的理解，并在相关情况下采用防止初始气流破坏的技术。

   NOTE: Watching video recordings of airflow visualization studies is very effective for increasing awareness of the impact of personnel movement and activities on the surrounding environment and the risk of contamination.

注：观看气流可视化研究的视频录像可有效提高对人员流动和活动对周围环境的影响以及污染风险的认识。

8. Training in those aspects of the pharmaceutical quality system that affect their job function as well as other relevant company policies, directives, and procedures
就药品质量体系中影响其工作职能的方面以及其他相关的公司政策、指令和程序进行培训。

Once the prerequisites are met, qualification may include levels of qualification permitting personnel to perform defined activities.
一旦满足了先决条件，资格确认可包括允许人员执行规定活动的资格等级。

Initial Aseptic Processing Personnel Qualification
无菌操作人员初始资格确认

Personnel successfully meeting initial aseptic processing qualification criteria should be permitted to participate in defined aseptic processing activities under direct supervision. The appropriate level of activities and level of supervision should be determined and recorded based on assessed relative risk of those activities. Personnel successfully completing the requirements of initial qualification should be qualified to perform aseptic processing activities that are less complex and assessed to be of lower risk but should always occur under direct supervision of a person who has attained advanced qualification (per the definitions described in this document).
应允许成功达到初始无菌操作资格标准的人员在直接监督下参与规定的无菌操作活动。应根据这些活动的相对风险评估结果，确定并记录适当的活动级别和监督级别。成功完成初始资格确认要求的人员应有资格执行复杂程度较低、经评估风险较低的无菌操作活动，但应始终在获得高级资格确认的人员（根据本文件所述定义）的直接监督下进行。

Initial Criteria
初始标准

To be considered initially qualified, personnel should have no observed lapses in the following:
要被视为初步确认合格，有关人员在以下方面不得有任何失误：

1. Prerequisites-related criteria, including demonstration of gowning proficiency, aseptic technique, and job functions
与先决条件相关的标准，包括展示穿无菌服熟练程度、无菌技术和工作职能

2. Demonstrated proficiency in aseptic technique by successfully completing a test involving expo- sure to nutrient media. The test should include manipulations and activities, including interventions, that are similar to those that will be undertaken during aseptic operations. The test can be associated with an APS in the process environment or can be performed in a simulated aseptic environment outside of the process environment.
通过成功完成涉及接触培养基的测试，证明已熟练掌握无菌技术。测试应包括与无菌操作过程中类似的操作和活动，包括干预。测试可与工艺环境中的 APS 相关联，也可在工艺环境之外的模拟无菌环境中进行。

3. Continuous, successful performance of aseptic processing activities for a period of time deemed appropriate by the company.

在公司认为适当的时间内，持续、成功地进行无菌操作活动。

Advanced Aseptic Processing Personnel Qualification
高级无菌操作人员资格确认

Personnel successfully completing advanced aseptic processing qualification criteria should be per- mitted to participate in aseptic processing activities with a lower level of supervision and/or perform activities that do not require direct supervision, depending on assessed risk.
成功完成高级无菌操作资格确认标准的人员，应根据评估的风险，允许在较低级别的监督下参与无菌操作活动和/或执行不需要直接监督的活动。

NOTE: High-risk interventions must always be supervised. Where a high-risk intervention is performed, the advanced personnel performing the intervention should be observed by another advanced operator to confirm that the intervention is performed correctly.
注：高风险干预必须始终有人监督。在执行高风险干预时，应由另一名高级操作员对执行干预的高级人员进行观察，以确认干预操作正确无误。

Advanced Criteria
高级标准

To be considered advanced qualified, personnel should have no observed lapses in the following:
要被视为高级合格人员，应在以下方面没有观察到失误：

1. Successful completion of initial qualification criteria, including prerequisites
   成功完成初始资格确认标准，包括先决条件

2. Successful completion of job training specific to advanced activities (e.g., activities that have been assessed to be of a medium to high risk of contamination.)
   成功完成专门针对高级活动的工作培训（例如，已被评估为具有中度至高度污染风险的活动）

3. Successful performance of simulated medium to high contamination-risk aseptic processes/activities outside of the APS for a period of time deemed appropriate by the company
   在公司认为适当的一段时间内，在 APS 之外成功执行模拟的中高污染风险无菌工艺/活动

4. Successful participation in a process APS run in which the personnel perform the same function(s) to the same extent as they will perform the function(s) during actual production (as applicable) to confirm that their aseptic process activity-related skills have not changed; these personnel would be qualified for activities considered to be higher risk
   成功参与工艺 APS 运行，在运行过程中，有关人员执行的功能与实际生产过程中将履行的职能相同（如适用），以确认其与无菌工艺活动相关的技能没有改变；这些人员将有资格从事被认为风险较高的活动。

Ongoing Aseptic Processing Personnel Assessment
持续的无菌操作人员评估

Qualification should include an ongoing personnel assessment designed to determine if the personnel remain in a qualified state. This should be part of the Aseptic Personnel Qualification Program and may include such steps as monitoring, observation, and supervisory feedback.
资格确认应包括持续的人员评估，以确定人员是否仍处于合格状态。这应该是无菌人员资格确认计划的 一

部分，可能包括监测、观察和监督反馈等步骤。

The ongoing personnel assessment program should be documented and should include:
持续的人员评估计划应记录在案，并应包括以下内容：

1. Specifying the frequency of and requirements for periodic requalification, or requalification after a prolonged absence, that permit personnel to continue to enter and participate in aseptic processing activities
规定定期重新确认或长期缺勤后重新确认的频率和要求，使人员能够继续进入和参与无菌操作活动。

2. Successful participation in APS runs in which they perform the same function(s) to the same extent as they will perform the function(s) during actual production (as applicable) at least once per year to maintain their qualification status and ensure that their aseptic process activity-related skills have not changed
每年至少参加一次成功的 APS 运行，在运行过程中执行与实际生产过程中执行功能相同的功能（如适用），以保持其资格确认状态，并确保其与无菌工艺活动相关的技能没有变化

3. Consideration of personnel-monitoring results, personnel-related deviations and failure investigations, job performance reviews, observations, absence from aseptic process job functions, and other information in the determination of qualification status.
在确定资格确认状态时，考虑人员监测结果、与人员有关的偏差和故障调查、工作绩效审查、观察结果、无菌工艺工作职能的缺失情况以及其他信息

Disqualification of Aseptic Processing Personnel
无菌操作人员的资格取消

The Aseptic Personnel Qualification Program should include criteria by which personnel lose their qualification status, which may include:
无菌操作人员资格确认计划应包括人员丧失资格确认的标准，其中可包括：

1. Failure to qualify or meet periodic qualification requirements
未取得资格确认或未达到定期资格确认要求
2. Participation in an unsuccessful or failed APS, where their performance was identified as a cause or contribution to the failure
参与了不成功或失败的 APS，其表现被认定是导致失败的原因或促成因素
3. Repeated aseptic processing performance in a manner deemed unacceptable in relation to clean- room or aseptic-process operations or functions.
在洁净室或无菌加工操作或功能方面以不可接受的方式重复进行无菌操作。
4. Failure to maintain gowning qualification
未能保持换无菌服资格确认
5. Failure to maintain training requirements
未达到培训要求
6. Repeated personnel monitoring excursions
多次人员监测偏离
7. Extended periods of inactivity or absence from the aseptic processing area.
长时间不活动或离开无菌操作区。
8. Other aspects of performance as identified by a supervisor (e.g., behavioral)
主管认定的其他方面的表现（如行为表现）

Requalification of Aseptic Processing Personnel following Disqualification
无菌操作人员被取消资格确认后的重新资格确认

The Aseptic Personnel Qualification Program should specify the conditions, requirements, and steps for personnel to be requalified following disqualification, and the criteria for reestablishing the person to a qualified status.
无菌人员资格确认计划应明确规定人员被取消资格确认后重新获得资格确认的条件、要求和步骤，以及重新确定人员获得资格确认的标准。

These criteria should depend on the reason and relative risk associated with the disqualification and may include:
这些标准应取决于取消资格确认的原因和相关风险，可包括：

1. Completion of specific CAPA actions
   完成具体的 CAPA 行动
2. Retraining in certain related topics
   某些相关主题的再培训
3. Repeat of gowning qualification
   重复穿无菌服资格确认
4. Successful personnel monitoring
   成功的人员监督
5. Participation in an aseptic-processing demonstration or successful APS runs
   参加无菌操作演示或成功运行 APS

Requalification after Prolonged Absence
长期缺勤后重新获得资格确认

Companies should establish and define the time period of a prolonged or extended absence that may affect the personnel's ability or proficiency to the degree it would require requalification. The requirement for repeating any of the prerequisites to qualification should be defined by the company.
公司应规定和界定长期或长期缺勤的时间期限，因为这可能会影响人员的能力或熟练程度，以至于需要重新进行资格确认。公司应规定重修任何资格确认先决条件的要求。

Access without Prior Qualification
无须事先获得资格确认即可访问

When situations arise in which nonqualified personnel (personnel who have not been deemed as qualified) are needed to enter into an aseptic processing area to transit through common aseptic areas to perform specified and approved activities, a procedure should be in place to address the controls required to allow such access. The procedure and controls required should be risk-based and will usually require a higher level of direct supervision, observation, and documentation.
当出现需要非合格人员（未被视为合格的人员）进入无菌操作区域，通过普通无菌区进行指定和批准的活动时，应制定程序来处理允许此类人员进入所需的控制措施。所需的程序和控制措施应以风险为基础，通常需要更高级别的直接监督、观察和记录。

The procedure controls for personnel accessing the aseptic processing area without prior qualification, at a minimum, should include:
对未经事先资格审查而进入无菌操作区域的人员的程序控制至少应包括：

1. Types of situations where nonqualified personnel are permitted to enter the aseptic area
   允许不合格人员进入无菌区的情况类型
2. Activities, including transit, these nonqualified personnel are permitted to perform
   允许这些不合格人员从事的活动，包括过境活动
3. Level of prior notice and approval required to allow these activities
   允许这些活动所需的事先通知和批准级别
4. Level of initial training required
   所需的初始培训水平
5. Level of direct supervision required
   所需的直接监督程度
6. Level of observation, monitoring, and reporting required
   所需的观察、监测和报告水平
7. Level of documentation and recording required of such access and activities undertaken during the access
   此类准入和准入期间开展的活动所需的文件和记录水平
8. Any subsequent actions required
   随后需要采取的任何行动

Rationale
理由

Personnel present and performing activities in the aseptic processing area present a risk of microbiological contamination, depending on their job function. They must be capable of adequately performing their job functions in a controlled manner. To do so and to control risk, they require specific training, skills, and an understanding of the process and impact of contamination, and they must be qualified to perform those functions.
在无菌操作区工作的人员有可能受到微生物污染，这取决于他们的工作职能。他们必须有能力以可控的方式充分履行其工作职能。要做到这一点并控制风险，他们需要接受专门的培训、掌握专门的技能、了解污染的过程和影响，而且他们必须具备履行这些职能的资格确认。

It is important that there is confidence in the ability of the aseptic personnel to have the knowledge and skills required to perform aseptic processing activities in a deliberate manner. Proper process design and training are a more effective means to ensure ongoing personnel performance than demonstration and testing. Interventions should be properly designed, qualified, and demonstrated (e.g., through air visualization studies) that they can be successfully performed by qualified and properly trained personnel. Demonstration and testing can be an effective way to provide this confidence. An APS, associated with the formal process APS or otherwise, or a similar set of tests, can be useful as a demonstration of those skills.
重要的是，要相信无菌人员有能力掌握必要的知识和技能，以审慎的方式开展无菌操作活动。与演示和测试相比，适当的工艺设计和培训是确保人员持续表现的更有效手段。应适当设计干预措施，使其合格，并证明（如通过气流可视化研究）合格和经过适当培训的人员可以成功地进行干预。演示和测试是提供这种信心的有效方法。与正式流程 APS 相关的 APS 或其他测试，或类似的一系列测试，都可以作为这些技能的演示。

Personnel qualification can be an effective means to establish personnel competency and exhibit skills that demonstrate the proficiency needed to reliably perform required activities. A written, formal qualification program that includes knowledge-related prerequisites and a means for demonstration can help ensure that

aseptic processing-area personnel have the proper training and knowledge for their respective activities.
人员资格确认是确定人员能力和展示技能的有效手段，可证明可靠地执行所需活动所需的熟练程度。一个书面的、正式的资格确认计划，包括与知识相关的先决条件和展示手段，可以帮助确保无菌操作领域的人员在各自的活动中获得适当的培训和知识。

This program should be risk-based, should include guidance, and should set reasonable criteria for acceptable qualification, disqualification, and requalification. It should be designed to minimize the risk of contamination from human activities, interventions, and inadequate aseptic techniques. The program should include prerequisites, define qualification procedures, and anticipate the need for disqualification procedures.
该计划应以风险为基础，应包括指导，并应为可接受的资格确认、资格确认取消和资格确认再审制定合理的标准。该计划应旨在最大限度地降低因人为活动、干预和不适当的无菌技术而造成污染的风险。该计划应包括先决条件，定义资格审查程序，并预测取消资格确认程序的需要。

It is important that personnel qualifications are not merely a demonstration of performance in an APS run. The APS is not sensitive enough to determine if the person is proficient and capable of reliably performing aseptic processing activities. At best, the APS, along with observation, can help identify flaws in the performance of personnel. In this case, reliance on the APS can result in limiting access to the cleanroom. This can hamper the ability of supervision to advance personnel training and observation. A phased approach, such as that described in the Aseptic Personnel Qualification Program section above, can allow for personnel access under specified levels of supervision commensurate with the relative risk of the activities to be performed. As such, it should be effective and aligned with current regulatory expectations.
重要的是，人员资格确认不仅仅是在 APS 运行中的表现。APS 的灵敏度不足以确定有关人员是否精通并能够可靠地执行无菌处理活动。充其量，APS 与观察相结合，可以帮助识别人员工作中的缺陷。在这种情况下，依赖 APS 可能会导致限制进入洁净室。这会妨碍监督人员推进人员培训和观察的能力。分阶段的方法（如上文无菌人员资格确认计划部分所述）可允许人员在特定级别的监管下进入洁净室，而监管级别应与要执行的活动的相对风险相称。因此，这种方法应该是有效的，并符合当前的监管要求。

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Topic C: Aseptic Processing Area Access Control

主题 C：无菌加工区进出控制

Problem Statement
问题陈述

How should manufacturers control access of personnel into the aseptic preparation and processing area?[1]
生产企业应如何控制人员进出无菌制备和加工区？[1]

Recommendation
建议

Control of access to the aseptic processing area should be in place through both procedures and physical controls. Preferably, this could be achieved during operations via electromechanical controls, such as access-card readers or biometric readers. Procedural controls may be appropriate in some operations, but justification for this practice should be documented. A dated and timed record should be maintained of all persons entering and leaving the aseptic processing area, subject to routine review by Quality Assurance personnel.
应通过程序控制和物理控制对进入无菌加工区进行控制。最好能在操作过程中通过机电化控制来实现，如门禁卡或生物识别。在某些操作中程序控制可能是合适的，但应有书面的记录说明其理由。应保存所有进出无菌加工区人员日期和时间的记录，并定期由质量保证人员进行审核。

Rationale
理由

Each person entering the aseptic processing area has the potential to introduce microbiological contamination. For this reason, controls should be in place to ensure that only designated persons access the aseptic processing area and a record of entrances and exits should be maintained for traceability and investigation, if necessary. The recording of time and date access is also important for data integrity considerations as it provides for accuracy and contemporaneousness of information.
每个进入无菌加工区的人都有可能引入微生物污染。因此，应采取控制措施，确保只有指定的人员才能进入无菌加工区，并应保留进出记录，以便在必要时进行追溯和调查。记录进出的时间和日期对于数据完整性来说也很重要，因为它提供了信息的准确性和时效性。

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[1] This section primarily addresses Grade A and B critical zones but should also address access to certain Grade C areas. A risk assessment could be utilized to determine the risk for Grade C areas.
本节主要涉及 A 级和 B 级关键区域，但也应涉及某些 C 级区域的进出控制。可以利用风险评估来确定 C 级洁净区的风险。

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Topic D: Performance of Environmental Monitoring

主题 D：环境监测的执行

Problem Statement
问题陈述
Who should perform EM?
谁应执行环境监测?

Recommendation
建议
Trained and qualified quality or production personnel can conduct EM.
受过培训的有资质的质量或生产人员可以执行环境监测。

The personnel performing the monitoring should receive training in good sampling practices, employing internal audits, unannounced monitoring, or random verification sampling by an independent quality unit to assess adherence to sampling practices.
进行环境监测的人员应接受良好取样规范方面的培训、内部审计、未经通知的监控或由独立的质量部门进行随机确证抽样，以评估是否遵守取样方法。

The Quality Unit is accountable for the effectiveness of the design and the performance of the EM system and is responsible for reviewing the data and ensuring the adequacy of the monitoring, including periodic observation according to approved procedures.
质量部门对环境监测系统设计和执行的有效性负责，并负责审查数据以及确保监测的充分性，包括根据批准的程序进行定期观察。

Rationale
理由
As with any procedure, individuals performing monitoring should be trained in the specific procedures. The goal is also to minimize the number of persons in the aseptic area and the concurrent risk of contamination.
与其他程序一样，进行监测的人员应接受特定程序的培训。目标还包括尽量减少无菌区域的人数和同时发生的污染风险。

As long as there are appropriate safeguards (i.e., effective training and periodic sampling oversight) in place, individuals from the production or Quality Unit may perform the sampling activity. However, it is the Quality Unit that is responsible for the oversight of the EM.
只要有适当的保障措施（即有效的培训和定期抽样监督），生产或质量部门的人员就可以进行取样活动。然而，负责监督 EM 的是质量部门。

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Topic E: Supervision in the Aseptic Processing Area

主题 E：无菌加工区的监管

Problem Statement
问题陈述

What is the degree of oversight necessary to effectively monitor an aseptic processing area?
怎样的监管力度才能有效监控无菌加工区？

Recommendation
建议

Oversight of aseptic processing should be performed by individuals who are trained, qualified, and experienced in the aseptic procedures for the areas being reviewed. These persons should have a thorough understanding of the process and the potential contamination risks. This oversight is best performed by physical presence in these areas with consideration on limiting microbial contamination risks (e.g., by monitoring the areas through windows or cameras when possible) as a result of additional supervisory personnel present in the aseptic processing area.
无菌加工的监督应由接受过培训、合格并具有相关经验的人员来进行。这些人员应对所检查区域的无菌程序和潜在的污染风险有深入的了解。这种监督最好亲自到达现场进行，同时也应考虑到控制微生物污染的风险（例如，在可能的情况下通过窗户或摄像头监测区域），以避免因额外的监督人员而增加的无菌加工区域的污染风险。

Aseptic processing areas that contain viewing windows may allow observation of some aspects of aseptic processing from outside the aseptic processing area.
包含观察窗的无菌加工区域可能允许从无菌加工区域之外观察无菌加工的某些方面。

The degree of oversight needed may depend on the level of physical separation of the operators from the exposed products and product-contact surfaces and the level of process automation.
所需的监督程度可能取决于操作员与暴露的产品和产品接触表面的物理隔离程度以及工艺自动化水平。

Proper oversight is required but not limited to cleaning, maintenance, production on all shifts, or any activity that can negatively impact the aseptic conditions within the aseptic processing area.
适当的监督是必需的，但不限于清洁、维护保养、各班次的生产，或任何可能对无菌加工区域内的无菌条件产生不良影响的活动。

The Quality Unit is also responsible for reviewing the oversight program for the aseptic area.
质量部门还负责审查无菌区域的监督计划。

Rationale
理由

Maintaining a successful aseptic operation is dependent on operational discipline and on the conduct of personnel in the way that they have been trained to perform, regardless of internal or external factors that may negatively influence their performance (e.g., pressure to complete a manufacturing run in a short time).

Manufacturers should be able to demonstrate that operational discipline is maintained, and oversight is a key methodology to achieve this.

维持成功的无菌操作取决于操作训练和人员按照培训要求的方式进行操作，而不受可能对他们的表现产生负面影响的内部或者外部因素（例如，为了在短时间内完成生产任务而面临的压力）。制造商应该能够证明自己的操作训练能够被维持，而监督是实现这一目标的关键方法。

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Topic F: Personnel Monitoring Frequency and Location

主题 F：人员监控的频次和位置

Problem Statement
问题陈述

What should be the frequency and sampling points of aseptically gowned personnel monitoring?
无菌更衣后人员监控的频次和采样点应该是多少?

Recommendation
建议

Monitoring of personnel in aseptic processing areas should be based on the evaluation of risk to products, product components, and product contact surfaces and to the specific process and systems (i.e., conventional, RABS, and isolator aseptic processing lines).
对无菌加工区域人员的监控应基于对产品、产品组件和产品接触表面以及特定工艺和系统（即常规、RABS和隔离器无菌生产线）的风险评估。

The sampling plans should be dynamic with monitoring frequencies and sampling locations and may be adjusted based on trend analysis. It is appropriate to increase or decrease sampling frequency based on this performance as long as a documented rationale is provided. Consideration should be given to the inclusion of periodic, unannounced personnel monitoring.
取样计划应随监控频次和位置而变化，并可根据趋势分析进行调整。只要提供书面的理由，就可以根据于此来适当增加或减少取样频次。还应考虑包括定期的、未经通知的的人员监控。

Sampling locations should be determined based on a risk evaluation and should be adequate to assess the contamination potential. For example, monitoring of gloves, forearms, and chests may be considered in filling lines and after such activities as assembly or open-door interventions of RABS, because these areas might be in the proximity of the exposed products or product-contact surfaces during interventions.
取样位置应根据风险评估确定，并应足以评估潜在的污染。例如，在灌装线上以及在RABS的组装或开门干预等活动之后，可以考虑监测手套、前臂和胸部，因为这些区域可能在干预期间接近暴露的产品或产品接触表面。

Minimally, gloves should be monitored each time an employee leaves an aseptic area (as noted in **Section IV, Topic A**: Glove Monitoring), and gown integrity should be checked upon entry and exit.
至少，每次员工离开无菌区域时都应监测手套（如第四部分，主题A：手套监测），进出时应检查洁净服的完整性。

If a gown breach is identified, the following should be performed:
如果发现洁净服破损，应执行以下操作:

- A quality notification/root cause analysis
  质量通知/根本原因分析
- Product impact assessment
  产品影响评估

- Additional monitoring at the site of the breach for investigational purposes, if considered relevant
  如果认为相关，出于调查目的在破损处进行额外监测。

Gown-sampling points may require monitoring as applicable to the process, and monitoring is required after critical manual interventions as justified in the CCS (EU Annex 1, Section 9.25).
洁净服取样点需要根据工艺进行监测，并且在CCS（欧盟附录1 9.25节）中所证明的关键手动干预操作后，需要进行监测。

Rationale
理由

Maintaining a successful aseptic operation is dependent on operational discipline and on personnel conduct in accordance with their training. Monitoring of gowning provides an early warning tool and allows the opportunity to react appropriately to unexpected changes to aseptic practices based upon variances in trends.
维持成功的无菌操作取决于操作训练和人员根据其培训的行为进行操作。对洁净服的监测提供了一种早期预警工具，并可以根据趋势变化中的差异，及时对无菌操作中的意外变化做出适当的反应。

Monitoring of gowning serves as a tool to demonstrate that personnel are adequately trained and are following procedures. Therefore, it is not necessary to monitor personnel to the same extent as they would be monitored during gowning certification every time they exit the aseptic processing area. While gowning certification locations are geared towards detecting whether personnel are able to appropriately don the garment, routine monitoring is geared toward understanding the aseptic behaviors in the area and if there were any risks to the aseptic process or product. Therefore, the monitoring of gloves is required at each event of significant intervention and upon exit from the aseptic area. Other gown monitoring locations should be included based on the risk-assessment criteria.
对洁净服的监测作为一个工具，证明人员经过充分培训并遵守程序的。因此，无需每次离开无菌加工区域时像确证时那样对人员洁净服进行监控。虽然洁净服取样位置确认旨在检测人员是否能够正确穿上洁净服，但常规监测旨在了解该区域的无菌行为以及无菌工艺或产品是否存在任何风险。因此，在每次重大干预事件和离开无菌区域时都需要监测手套。其他洁净服的监测位置应根据风险评估来确定。

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Topic G: Sterile Gown Usage

主题 G：无菌洁净服的使用

Problem Statement
问题陈述

Must a sterile gown be used for each entry into the aseptic processing area?
每次进入无菌加工区时都必须使用无菌洁净服吗?

Recommendation
建议

A sterile gown must be used for each entry into the aseptic processing area. A sterile gown is defined as a gown from a sealed package that has not been previously worn since sterilization. A sterile gown should be changed whenever the integrity of the gown might be compromised. The maximum time usage during a single entry of the sterile gown and maximum number of times a single gown can be washed and sterilized should be determined and defined.
每次进入无菌加工区时都必须使用无菌洁净服。无菌洁净服被定义为自灭菌以来从未穿过的放置在密封包装中的洁净服。每当洁净服的完整性可能受损时，应更换无菌洁净服。应确定和定义无菌洁净服单次穿着时间最长时间，使用以及单件洁净服可以被清洗和消毒的最大次数。

Rationale
理由

The major source of microbial contamination of aseptic processing areas is personnel. Gowning is the most direct and significant environmental control measure that can be employed to control contamination derived from personnel. During the time the sterile gown is worn for each usage, the efficiency of the sterile gown decreases, therefore, the length of time the gown is worn must be controlled. In addition, repeated washing and sterilization of the gown causes degradation, therefore, the number of sterile gown processing cycles must be controlled.
无菌加工区的主要微生物污染源是人员。洁净服是可用于控制人员污染的最直接和最重要的环境控制措施。在每次使用无菌洁净服期间，无菌洁净服的效率会降低，因此，必须控制其穿着的时间长度。此外，对洁净服的反复洗涤和灭菌会导致其损害，因此，必须控制无菌洁净服的处理数。

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Topic H: Occupancy in the Aseptic Processing Area

主题 H：无菌加工区域的使用时间

Problem Statement
问题陈述

What is the proper number of people to be present in an aseptic processing area?
进入无菌加工区的适当人数是多少?

Recommendation
建议

The number of personnel required to safely and effectively perform and supervise aseptic processing activities should be determined and defined. The number of required personnel will depend on the type of activity being performed. This number may represent a maximum or a minimum number of people required.
应确定和定义安全有效地执行和监督无菌加工活动所需的人员数量。所需人员的数量将取决于所执行的活动类型。此数字可能代表所需的最大或最小人数。

Only the number of personnel required to perform and supervise the ongoing aseptic processing activities should be present in the respective aseptic processing areas. This also applies to ancillary areas such as airlocks and corridors.
在各自的无菌加工区中，只应有执行和监督正在进行的无菌加工活动所需的人员数量。这也适用于气闸和走廊等辅助区域。

The maximum number of qualified personnel allowed in a given room should depend on the classification of the area and should be verified through EM and process simulations.
允许进入指定房间的最多人员数量应取决于洁净区的级别，并应通过EM和工艺模拟来进行验证。

Rationale
理由

Personnel constitute the greatest risk to an aseptic manufacturing process from a microbiological perspective; however, the number of people must be adequate to perform the process with a proper level of attention and activity consistent with good aseptic technique. In general, the minimal number of personnel should be present to carry out such aseptic manufacturing processes.
从微生物的角度来看，人员是构成无菌生产过程最大的风险；但是，人数必须足以以适当的注意力和活动水平执行该工艺，并符合良好的无菌技术。一般来说，应该有最少数量的人员来执行这种无菌生产过程。

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Topic I: Personnel Practices for Hygiene and Hand Washing

主题 I：人员卫生和洗手规范

Problem Statement
问题陈述

What are the allowable personnel-related conditions for gowning and entering a cleanroom?
人员更衣和进入洁净室的允许条件是什么?

Recommendation
建议

Personnel entering cleanrooms during periods of operation should be free of conditions that pose a high risk of compromise to the purity and safety (i.e., sterility) of the product.
在生产期间进入洁净室的人员，进入洁净室的人员不应处于对产品的纯度和安全性（即无菌性）构成高风险的环境中。

Personnel should demonstrate a high degree of personal hygiene, cleanliness, and precautions, including but not limited to the following:
人员应表现出高度的个人卫生、清洁和预防措施，包括但不限于以下内容:

- Personnel should not wear jewelry (i.e., rings, bracelets, piercings, or wristwatches) or other items that could tear gloves, gowns, boots, hoods, or masks or could otherwise pose a safety hazard or process contamination risk.
  人员不应佩戴珠宝（即戒指、手镯、耳环或手表）或其他可能撕裂手套、洁净服、靴子、头罩或口罩的物品，或以其他方式构成安全隐患或工艺污染风险的物品。
- Personnel garments worn under the gown should not contribute fiber or microbiological contamination beyond the ability of the gown or boots to contain it.
  穿戴在洁净服下的人员服装不应造成纤维或微生物污染，超过洁净服或靴子所能够覆盖的范围;
- Personnel should wear garments under gowns that minimize perspiration yet are sufficient for personal comfort and warmth.
  工作人员应在洁净服下穿保持个人舒适和温暖的衣服，尽量减少出汗。
- Personnel should wear dedicated shoes or footwear that are not worn outside of the cleanroom area.
  人员应穿戴专用的鞋子或鞋具，且不能穿到洁净室外;
- Dedicated cleanroom socks need to be worn. If worn, personnel should remove personal socks prior to donning dedicated cleanroom socks.
  需要穿专用的洁净室袜子。如果穿戴个人的袜子，则人员应在穿戴专用袜子前将个人的袜子脱下来。
- Personnel should not wear boots or shoes under gown boots that could tear the gown or contribute contamination.
  工作人员不应在洁净鞋内穿靴子或鞋子，以免撕裂洁净服或造成污染。
- Personnel should not wear perfume, makeup, volatile chemicals, or flaking substances that could contaminate products.
  人员不应使用可能污染产品的香水、化妆品、挥发性化学物质或可能会脱落的物质。
- Personnel who require visual aids and work routinely in the cleanroom should be allocated

prescription glasses that can be sanitized without degradation. Transient visitors should water-and-soap wash their glasses at the hand sanitation station and not approach the critical zone.
需要视觉辅助设备并经常在洁净室工作的人员，应配戴可消毒且不会损坏的度数眼镜。临时访客应在手消毒站用水和肥皂清洗眼镜，且不要接近关键区域。

- Personnel should wash and sanitize their hands prior to gowning but not use types of soap or sanitizing agents that dry the skin or cause skin to flake.
工作人员应在穿洁净服前洗手和消毒，但不要使用会使皮肤干燥或导致皮肤脱屑屑的肥皂或消毒剂。
- Personnel should have open cuts, abrasions, or freshly applied tattoos on their skin covered with bandages or other means and should not enter the aseptic processing area if it is determined that the extent of those conditions could still pose risks of environmental or product contamination.
人员的皮肤上如果有开放性伤口、擦伤或刚做的的纹身，应使用绷带或其他方式覆盖，如果确定这样做以后仍然能够造成环境或者产品污染的风险，则不应该进入无菌加工区域。
- Personnel with respiratory illnesses, open lesions, or other potentially infectious conditions that could pose a higher risk of environmental or product microbiological contamination and the risk of spreading contagious pathogens should not be permitted in the aseptic area.
患有呼吸道疾病、开放性病变或其他潜在传染性疾病的人员，可能造成更高的环境或产品微生物污染风险以及传播传染性病原体的风险，不应进入无菌区域。

Rationale
理由

Personnel represent a potential source of microbiological and chemical contamination. Therefore, precautions should be employed to minimize the risk of contaminating the environment or the product. These precautions should be commensurate with the level of risk of contamination. These precautions should take into consideration the risk to product quality with personnel safety and the ability of people to perform their work functions.
人是微生物和化学污染的潜在来源。因此，应采取预防措施，以最大程度减少污染环境或产品的风险。这些预防措施应与污染风险水平相称。这些预防措施应考虑到产品质量的风险，人员安全和人员履行工作职能的能力之间的平衡。

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V. Material Transfer 物料转运

Topic A: Entry of Equipment and Material into an Aseptic Processing Area

主题 A：设备和材料进入无菌生产区

Problem Statement
问题陈述

What must be done when materials and/or equipment are being transferred into a Grade A and Grade B aseptic processing area?
当材料和/或设备被转移到 A 级和 B 级无菌生产区时，必须做些什么?

Recommendation
建议

Sterilized materials and equipment should be transferred into the Grade A and Grade B aseptic processing area using the following methods and taking these precautions:
已灭菌材料和设备应使用以下方法并采取以下预防措施转移到 A 级和 B 级无菌生产区:

- The preferred method for transferring sterilized materials and/or equipment into an aseptic processing area is by using a unidirectional sterilization process (e.g., through an attached double- door autoclave or a depyrogenation tunnel) where materials or equipment cannot be sterilized directly into Grade A, they must be transferred into and through the Grade B area while being protected from particulate and microbiological contamination e.g., multiple wrapping.
  将已灭菌材料和/或设备转移到无菌生产区的首选方法是使用单向灭菌工艺 （例如，通过连接的双扉高压灭菌器或除热原隧道），在这种情况下，材料或设备不能直接进入 A 级区域灭菌，而必须转移到并穿过 B 级区域，同时还要防止微粒和微生物污染（例如，多重包装）。

- Pre-sterilized items that are transferred into the Grade A and Grade B area should be contained in sealed packaging and disinfected prior to transfer into the Grade B area and subsequent transfer into the Grade A area. The integrity of the packaging should be qualified and visually verified prior to use. The packaging material should be compatible with the disinfecting method and agent. Multiple layers of protective wrapping material should be sequentially removed as the items are transferred from areas of lesser to greater control (e.g., Grade C to Grade B, Grade B to Grade A). Where possible, the use of rapid transfer port technology should also be considered.
  转入 A 级和 B 级区域的预灭菌物品应装在密封包装内，并在转入 B 级区域和随后转入 A 级区域前进行消毒。在使用前，应对包装的完整性进行确认和目检。包装材料应与消毒方法和消毒剂兼容。当物品从控制程度较低的区域转移到控制程度较高的区域时(例如，C 级转移到 B 级，B 级转移到 A 级)，应依次去除多层保护包装材料。在可能的情况下，还应考虑使用快速转移端口技术。

- Items that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the packaging allows the items to be disinfected during transfer into grade A (e.g., by use of multiple layers that can be removed at each transfer from areas of lesser to greater control).
  如果包装的完整性和结构允许物品在转入 A 级时进行消毒（例如，使用多层包装，每次从控制较弱的区域转入控制较强的区域时都可以去除多层包装），则使用多层无菌包装的物品不需要储存在洁净室中。

- Where materials and/or equipment are sterilized in sealed packaging and then transferred into the area, this must be done, for example, via airlocks or pass-through hatches with accompanying disinfection of the exterior of the transfer packaging.
  如果材料和/或设备在密封包装中消毒，然后转移到区域内，则必须通过气闸或传递窗等方式进行，并对转移包装的外部进行消毒。

- For materials and/or equipment that are necessary for aseptic processing but are not amenable to sterilization (e.g., lubricant containers or electronic instruments), an effective and validated dis- infection process must be in place. If possible, equipment should remain in the aseptic processing area to minimize the risk of repeated transfers.
  对于无菌生产所需但无法进行灭菌的材料和/或设备（如润滑剂容器或电子仪器），必须制定有效且经过验证的消毒程序。如果可能，设备应留在无菌生产区，以尽量减少重复转移的风险。

- Only items that are on an approved list should be allowed to be transferred into the Grade A and Grade B area via the air lock. Any unapproved items that require transfer should be covered by a deviation that includes a specific sanitization and monitoring regime derived by consultation with quality assurance and microbiology personnel.
  只有被列入批准清单上的物品才可通过气闸转移到 A 级和 B 级区域。任何需要转移而未经批准的物品都应属于偏离，需要有质量保证和微生物学人员协商制定的具体消毒和监测制度。

Rationale
理由

Materials and equipment entering a Grade A and Grade B area may pose a risk of introducing microbiological contamination. Therefore, precautions must be taken to reduce the risk of contamination of the sterilized materials and equipment and of the Grade A and Grade B environment.
进入 A 级和 B 级区域的材料和设备可能会带来微生物污染的风险。因此，必须采取预防措施，降低灭菌材料和设备以及 A 级和 B 级环境受到污染的风险。

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Topic B: Sterile Hold Times for Materials

主题 B：材料的无菌保存时间

Problem Statement
问题陈述

How should sterilized material (e.g., sterilized equipment, utensils, components) hold times be developed and implemented?
如何制定和实施已灭菌材料（如灭菌设备、器皿、组件）的保存时间？

Recommendation
建议

A sterilized material hold-time period should be developed by an assessment of the conditions under which the sterilized material and its packaging will be held and of the anticipated use requirements of the process.
应通过评估已灭菌材料及其包装的保存条件和工艺的预期使用要求来确定灭菌材料的保存期。

A material that has been appropriately sterilized can be expected to remain so indefinitely within the Grade A and Grade B environments until and unless the sterile protective barrier is compromised. For material going into an isolator, controlled storage (e.g., storage which prevents damage to the wrap- ping) within a Grade C environment is necessary and appropriate.
经过适当灭菌的材料在 A 级和 B 级环境中可以无限期地保持无菌状态，除非无菌保护屏障受到破坏。对于进入隔离器的材料，在 C 级环境中进行受控储存（如防止包装损坏的储存）是必要和适当的。

Because the demands of barrier methods, materials, storage conditions, and processes vary, acceptable hold times, even for similar materials, can vary widely.
由于对阻隔方式、材料、储存条件和工艺的要求各不相同，因此即使是类似的材料，可接受的保存时间也会有很大差异。

The integrity of the sterile protective barrier should be qualified in APS for the maximum hold time, and the process should include inspection of each sterile item prior to its use to ensure that the sterile protective measures have remained intact. In the case of wrapping that is heat-sealed, the heat-sealing process should be qualified.
无菌保护屏障的完整性应在 APS 中对最长保持时间进行确认，该过程应包括在使用前对每个无菌物品进行检查，以确保无菌保护措施保持完好。如果包装是热封的，则热封工艺应合格。

For materials that are sterilized within a rapid transfer port canister (material for use with RABS or an isolator), a vent filter must be employed to allow vapor transfer in and out of the canister during autoclaving. In these cases, integrity testing of the filter post-use must be performed. In addition, a visual inspection of the integrity of the canister should also be performed.
对于在快速转移端口罐内灭菌的材料（与 RABS 或隔离器一起使用的材料），必须使用通气过滤器，以便在高压灭菌期间允许蒸汽进出罐。在这种情况下，必须在使用后对过滤器进行完整性测试。此外，还应对罐的完整性进行目视检查。

Rationale for Recommendation
建议的理由

Sterilized materials will remain sterile indefinitely until they are exposed to contaminants. The means by which sterile materials become contaminated is degradation, damage, or failure of the sterile barrier system. The ability to maintain the barrier and to detect barrier failure is the critical factor, not time. Because the main critical factor in packaging integrity is not time but rather handling and storage, which is visually inspected at every run, a single APS is appropriate to support hold time. However, the aging of wrapping materials may be a contributing factor to barrier deterioration.

已灭菌材料在暴露于污染物之前将无限期地保持无菌状态。灭菌材料受污染的途径是无菌保障系统退化、损坏或失效。保持屏障和检测屏障失效的能力是关键因素，而不是时间。由于影响包装完整性的主要关键因素不是时间，而是每次运行时都要进行目视检查的处理和储存，因此使用单个 APS 来支持保持时间是合适的。然而，包装材料的老化可能是导致屏障退化的一个因素。

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VI. Cleaning, Disinfection, and Sterilization

清洁、消毒和灭菌

Topic A: Disinfection Program

主题 A：消毒程序

Problem Statement
问题陈述
Is a disinfectant rotation program necessary?
是否有必要实施消毒剂轮换程序?

Recommendation
建议
A disinfectant rotation program is not necessary; however, the use of disinfectants and sporicidal agents, where the agents are alternated on a defined schedule, may be an effective approach to the cleanroom disinfection program.
消毒剂轮换程序是没有必要的；不过，使用消毒剂和杀孢子剂，按照规定的时间表交替使用，可能是洁净室消毒程序的有效方法。

The disinfection program should be shown to be effective against anticipated levels of surface contaminants, bacteria, and fungi.
应证明消毒程序对预期水平的表面污染物、细菌和真菌有效。

The disinfection program should be based on assessed risk to sterile product. More than one type of disinfecting agent should be used, including the periodic usage of a sporicidal agent. The selection and frequency of cleanroom disinfectants, including sporicidal agents, should be based on EM data (quantitative/qualitative), trends, cleanroom materials, and the efficacy of the disinfectant procedures. A typical program would include the frequent use of a disinfectant agent with the less frequent use of a sporicidal agent; however, the unique filling operation must be taken into consideration to best determine which agents to select for the facility.
消毒程序应基于对无菌产品的风险评估。应使用一种以上的消毒剂，包括定期使用杀孢子剂。洁净室消毒剂（包括杀孢子剂）的选择和使用频率应基于 EM 数据（定量/定性）、趋势、洁净室材料以及消毒程序的效力。典型的程序包括经常使用消毒剂和低频率使用杀孢子剂；但是，必须考虑到具体的灌装操作，以最好地确定为设备选择何种消毒剂。

Each manufacturer should have a formal program governing the qualification, use, and disposal of disinfectants. This program should include the rationale for disinfectant or sporicidal agent use.
每个制造商都应该有一个正式的程序来管理消毒剂的确认、使用和处理。该程序应包括消毒剂或杀孢子剂使用的基本原理。

The disinfectant program should be periodically evaluated and modified or maintained based on the use of area classification, review of EM data, and risk assessment.
应根据区域级别、EM 数据审查和风险评估，定期评估和修改或维护消毒程序。

For isolators, the bio-decontamination process should include a sporicidal agent in a gaseous or vaporized

form. For RABS, the disinfection should include the routine application of a sporicidal agent. The sporicidal agents and frequency of application should take into consideration adverse effects on equipment and material surfaces. Disinfectant supplier safety recommendations and precautions should also be followed to protect personnel from harmful effects of exposure to sporicidal agents.
对于隔离器，生物消毒程序应包括气态或汽态杀孢子剂。对于 RABS，消毒应包括常规应用杀孢子剂的过程。杀孢子剂和使用频率应考虑到对设备和材料表面的不利影响。还应遵守消毒剂供应商的安全建议和预防措施，以保护人员免受接触杀孢子剂的有害影响。

Rationale
理由

Cleanroom disinfectants are used to maintain control over the contamination level of the cleanroom environment. To be effective, cleanroom disinfectants should be matched to the anticipated level of contamination.
洁净室消毒剂用于控制洁净室环境的污染水平。洁净室消毒剂应与预期的污染程度相匹配，才能发挥有效作用。

While it is not proven that microorganisms develop resistance to particular agents, the use of different agents and the rotation between disinfectants and sporicides results in the destruction of a broader range of potential environmental contaminants, including bacterial spore-formers. The exclusive use of sporicidal agents may be an effective microbiological approach in the short term, however, the corrosion that might result from this practice could present additional risk of cleanroom and equipment damage.
虽然尚未证明微生物会对特定的药剂产生抗药性，但使用不同的药剂以及在消毒剂和杀孢子剂之间轮换使用，可以消灭更多潜在的环境污染物，包括产芽孢细菌。在短期内，完全使用杀孢子剂可能是一种有效的微生物处理方法，然而，这种做法可能导致的腐蚀可能会带来洁净室和设备损坏的额外风险。

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Topic B: Sterilization of Sanitizers, Disinfectants, and Cleaning Agents

主题 B：杀菌剂、消毒剂和清洁剂的灭菌法

Problem Statement
问题陈述

How do you ensure that sanitizers, disinfectants, and cleaning agents (detergents) used in aseptic processing areas (Grade A and Grade B) are free from contaminants?
如何确保无菌生产区（A 级和 B 级）使用的杀菌剂、消毒剂和清洁剂（洗涤剂）不含污染物?

Recommendation
建议

Sanitizers, disinfectants, and cleaning agents used in Grade A and Grade B areas should be sterile. These agents used in Grade C and Grade D may also be required to be sterile where determined in the CCS. Where sanitizers, disinfectants, and cleaning agents are diluted, prepared, and sterilized by the sterile product manufacturer, this should be done in a validated manner to prevent contamination and they should be monitored for microbial contamination. The sterilization of these prepared agents is typically performed using 0.2 µm or smaller porosity.
A 级和 B 级区域使用的杀菌剂、消毒剂和清洁剂应是无菌的。在 CCS 中确定的情况下，C 级和 D 级中使用的这些试剂也可能需要无菌。如果杀菌剂、消毒剂和清洁剂是由无菌产品生产商稀释、配制和灭菌的，则应采用经过验证的方式进行，以防止污染，并应对微生物污染进行监控。这些制备的试剂灭菌通常使用 0.2 µm 或更小的孔径。

Sterile sanitizers, disinfectants, and cleaning agents should be maintained in an environment that maintains this condition. The filtered agents should be stored in sterilized closed containers until use. The period of time from the filtration to the use, and duration of use should be qualified.
无菌杀菌剂、消毒剂和清洁剂应存放在能保持这种状态的环境中。过滤后的药剂应储存在灭菌的密闭容器中，直至使用。从过滤到使用的时间段以及使用期限内都应符合要求。

For Grade A, single-use, sterile sanitizers, disinfectants, and cleaning agents are recommended for use, either within spray-flasks, pressurized spray cans, wipes, or other applicators and containers. When using reusable spray flasks, steps should be taken to ensure that the spray flasks can be re-sterilized and have not been compromised by air drawn back into the container during use.
对于 A 级，建议在喷瓶、加压喷罐、湿巾或其他涂抹器和容器中使用一次性无菌杀菌剂、 消毒剂和清洁剂。在使用可重复使用的喷壶时，应采取措施确保喷壶可以重新灭菌，并且在使用过程中不会因空气被吸入容器而受到污染。

For purchased sanitizers, disinfectants, and cleaning agent manufacturer's instructions should be fol- lowed and certificates of analysis reviewed and documented.
对于购买的杀菌剂、消毒剂和清洁剂，应遵守制造商的说明，并审查和记录分析证书。

NOTE: It is not necessary to perform a sterility test of purchased, ready-to-use and sterile sanitizers, disinfectants, and cleaning agents. This is generally based on an audit of the supplier, knowledge of the

supplier's processes and testing. Without that confidence, there might need to be some confirmatory testing even if on skip lot.

注：无需对购买的即用型无菌杀菌剂、消毒剂和清洁剂进行无菌测试。这通常是基于对供应商的审计、对供应商工艺和检测的了解。如果没有这种信心，可能需要进行一些确证性测试，即使是跳过批次。

Unless there is evidence to the contrary, the sterilization of sporicides and sporicidal agents may not be necessary because they are considered to be "self-sterilizing agents."

除非有相反的证据，否则可能没有必要对杀孢子剂和杀孢子的药剂进行灭菌，因为它们被认为是 "自灭菌试剂"。

Rationale

理由

The sterilization procedure by the supplier, or the sterile filtration process and holding procedure at the manufacturers should be adequate to render the disinfectants and cleaning agents free of contamination, since these solutions are inherently low-bioburden.

供应商的灭菌程序或制造商的无菌过滤程序和保持程序应足以使消毒剂和清洁剂不受污染，因为这些溶液本身具有低生物负荷的特性。

Once a qualified process has been put in place, the sterility test would not add any further level of assurance for ready-for-use or purchased sanitizers, disinfectants, or cleaning agents.

一旦执行了合格的工艺，无菌检测就不会对即用型或外购的杀菌剂、消毒剂或清洁剂增加任何进一步的保险水平。

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Topic C: Hold Times for Sterilized Wrapped Parts, Components, and Other Material

主题 C：无菌包装部件、组件和其他材料的保持时间

Problem Statement
问题陈述

How should hold times be determined for sterilized wrapped parts, components, and other material?
如何确定无菌包装部件、组件和其他材料的保持时间？

Recommendation
建议

Preference should be given to the use of packages that are preformed and sealed over wrapping that is folded and taped.
应优先使用预成型并密封在折叠和胶带包裹上的包装。

The date of sterilization and the expiry date should be identified on each package. A maximum hold time should be set consistent with the needs of the process and supported based on the qualification of the wrapping method.
每个包装上都应标明灭菌日期和有效期。应根据工艺的需要设定最长保持时间，并经过包装方式的确认。

The qualification is based on:
确认基于：

- Barrier property of the wrapping material
  包装材料的阻隔性能
- Qualified wrapping, handling and storage procedure
  合格的包装、处理和储存程序
- Quality of the handling and storage environment
  处理和储存环境的质量

Using wrapped materials in one or more media fills that have been held for the maximum hold time might be an additional step to ensure package integrity in initial qualification; however, media fills alone will not be sufficient or may not be necessary to qualify the holding time of wrapped material.
在一次或多次培养基灌装中使用已保持最长保存时间的包装材料，可能是在初始确认中确保包装完整性的额外步骤；但是，仅靠培养基灌装不足以或可能没有必要来确认包装材料的保持时间。

Rationale for Recommendation
建议的理由

The variables in sterilized material hold times are wrapping method, closing and sealing method, handling conditions, storage conditions and microbial barrier capability and integrity. If the barrier materials remain dry post-sterilization, the risk of contamination is low. If the procedure is sound, then time should not be a factor unless the wrapping materials degrade or are damaged over time, and as such maximum hold times

do not require revalidation unless changes are made to the materials or sterilization cycle/method used. However, a maximum hold time is recommended because open-ended times may introduce unforeseen variables.

灭菌材料保持时间的可变因素包括包装方法、封闭和密封方法、处理条件、储存条件以及微生物阻隔能力和完整性。如果屏障材料在灭菌后保持干燥，污染的风险就很低。如果程序是合理的，那么时间不应该是一个因素，除非包装材料随着时间的推移而降解或损坏，因此，除非对材料或所使用的灭菌周期/方法进行了更改，否则不需要重新验证最长保持时间。不过，建议使用最长保持时间，因为开放式的时间可能会带来不可预见的变数。

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Topic D: Frequency of Requalification of Sterilization Processes

主题 D：灭菌工艺再确认频率

Problem Statement
问题陈述
How frequently should sterilization processes be requalified?
灭菌工艺应多久再确认一次?

NOTE: Radiation sterilization is not in scope for this topic.
注：辐射灭菌不在本主题的范围内。

Recommendation
建议
A successful sterilization process validation program is one that is initiated early in the product lifecycle and is ongoing until the process or product reaches the end of that lifecycle. Comprehensive written procedures that define the expectations and commitment to process validation lifecycle principles is the foundation of a successful validation program. This policy should define the quality management philosophy, components of validation, periodic review or requalification time frames, documentation requirements (including a process validation master plan), validation protocols and reports, and responsibilities of key stakeholders within the organization.
一个成功的灭菌工艺验证程序应在产品生命周期的早期启动，并一直持续到工艺或产品生命周期结束。全面的书面程序规定了对工艺验证生命周期原则的期望和承诺，是成功验证程序的基础。该程序应明确质量管理理念、验证的组成部分、定期审核或重新验证的时间框架、文件要求（包括工艺验证总计划）、验证协议和报告，以及组织内主要利益相关者的责任。

Any change in equipment or process should be evaluated for its impact on process qualification and, if necessary, requalified. Requalification should be performed on a regular basis (typically every 12 months) to ensure there has not been an undetected change in product or process. Requalification should be performed using the same operational parameters and acceptance criteria as the original qualification runs. Supporting documentation for tests performed under the process qualification pro- gram should include, as applicable, information outlined in the original qualification effort.
应评估设备或工艺的任何变更对工艺确认的影响，如有必要，应重新确认。应定期（通常每 12 个月）进行再确认，以确保产品或工艺中没有未发现的变化。应使用与最初确认运行相同的操作参数和验收标准进行重新确认。根据工艺确认程序进行试验的支持文件应包括原始确认工作中概述的信息（如适用）。

For terminal sterilization, verification of acceptable steam quality for porous/hard goods load sterilization should also be performed at this time.[1] Results of the requalification study should demonstrate that the sterilizer's performance has not changed since the original effort. All sterilizer load(s) should be periodically included in requalification runs. Where equivalence has been established between sterilizers, a risk-based reduction in requalification activity may be considered.

[1] The quality of the sterilizing agent should also be confirmed on a regular basis.
消毒剂的质量也应定期确认。

对于终端灭菌，此时还应验证多孔/硬质物品装载灭菌的可接受蒸汽质量。再确认研究的结果应表明，自最初的确认行动以来，灭菌器的性能没有改变。所有灭菌装载应定期纳入再确认运行。如果已确定灭菌器之间具有等效性，则可考虑根据风险减少再确认活动。

Requalification should also include review of performance data from various monitoring sources (e.g., engineering, maintenance, calibration data) of sterilizers and supporting equipment to verify that there have been no adverse trends or drifts away from the baseline performance established during validation. A review of change-control documentation should be conducted as part of the requalification.
再确认还应包括审查灭菌器和辅助设备的各种监测来源（如工程、维护、校准数据）的性能数据，以验证没有不良趋势或偏离验证期间建立的基线性能。作为再确认的一部分，应对变更控制文件进行审查。

Rationale
理由

A qualified process is one where there is a high degree of assurance that a process will be repeatable unless a change is made. Any changes to the process or equipment should be assessed and requalified prior to implementation of changes.
一个合格的工艺是一个高度保证过程可重复的工艺，除非发生变更。对工艺或设备的任何变更都应进行评估，并在实施变更之前重新确认。

The purpose of periodic requalification is to identify undetected changes and variables to the process that have the potential to negatively impact efficacy. Since the sterilization process is complex and the impact of a failure is severe, periodic assessment and revalidation is required. The basis for the revalidation frequency should emphasize process performance and control with focus on the level of variability in the delivery of key and critical parameters.
定期再确认的目的是识别工艺中可能对效果产生负面影响的未检测到的变化和可变因素。由于灭菌工艺复杂，失败的影响严重，因此需要定期评估和再验证。再验证频率的依据应强调工艺性能和控制，重点是关键和重要参数的变化程度。

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Topic E：Porous/Hard Goods Sterilization Process Qualification

主题 E：多孔/硬质物品灭菌工艺确认

Problem Statement
问题陈述
Should discrete loading patterns be established for all moist-heat sterilization processes?
是否应为所有湿热灭菌工艺建立分别的装载模式?

Recommendation
建议
The loading pattern should be established for all moist-heat sterilization processes from the knowledge of the materials and equipment and verified as part of process qualification. In some cases, a minimum-maximum bracketing approach may be acceptable where studies (e.g., cycle development studies) indicate that the positioning and inclusion of materials in loads that fall between the minimum and maximum does not present more of a sterilization challenge than the qualified minimum-maximum load.
应根据对物料和设备的了解，为所有湿热灭菌工艺建立装载模式，并作为工艺确认的一部分进行验证。在某些情况下，如果研究（例如：循环开发研究）表明，在最大和最小装载之间的装载物的定位和包括的装载物不会比经过确认的最小-最大装载带来更大的灭菌挑战，则可以接受最小-最大括号法。

Considerations should be given to the positioning and location of materials within the load. Discrete loading patterns may not be necessary if it can be demonstrated that cycle efficacy is not affected by variable loading patterns.
应考虑装载中物品的定位和位置。如果可以证明不同的装载模式不会影响循环效力，则可能不需要采用分别的装载模式。

Rationale
理由
Reproducibility in moist-heat sterilization is dependent upon the capability of the sterilization process to consistently deliver process efficacy for the stated loading pattern(s).
湿热灭菌的再现性取决于灭菌工艺在规定的装载模式下持续提供工艺效力的能力。

The ability of the cycle to sterilize materials is dependent on the positioning and location of those materials in the sterilizer and may not necessarily be affected by the volume of materials in the sterilizer.
循环对物料的灭菌能力取决于这些物料在灭菌器中的定位和位置，而不一定受灭菌器中物料体积的影响。

The materials of the load should be oriented to ensure proper air removal, steam penetration and condensate removal.
应调整装载的物料的方向，以确保完全地排除空气、蒸汽渗透和冷凝水排除。

A more detailed discussion on establishing loading patterns can be found in *Technical Report No. 1 (Revised 2007): Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control.*

关于建立装载模式的更详细的讨论可以在*技术报告 1（2007 年修订）：湿热灭菌工艺的验证：循环设计、开发、确认和持续控制中找到。*

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Topic F: Integrity Testing of 0.2 Micron Filters

主题 F：0.2 微米过滤器的完整性测试

Problem Statement
问题陈述

Should 0.2 µm filters used for purposes other than sterilization (e.g., prefiltration, bioload/bioburden reduction, redundant filters[1] backup) be integrity-tested?

用于除灭菌以外目的的 0.2 微米过滤器（例如：预过滤、降低生物负荷/生物负载、备用冗余过滤器[2]）是否应进行完整性测试？

Recommendation
建议

The 0.2 µm filters used for purposes other than the sterilization of fluids can be and are used to re duce bioburden and/or protect other process equipment, for example, chromatography columns. The necessity to test the integrity of such filters should be determined using appropriate risk assessments, which include testing the function of the filter, the position, and the criticality within the process.

用于液体灭菌以外目的的 0.2 微米过滤器可以并且用于降低生物负载和/或保护其他工艺设备，例如色谱柱。应使用适当的风险评估来确定是否有必要测试此类过滤器的完整性，其中包括测试过滤器的功能、位置以及在工艺中的关键性。

Rationale
理由

The decision to test the integrity of a bioburden-reducing 0.2 µm-rated filter should be left to the discretion of the filter user. In some instances, the filter is used to protect another process step or as a prefilter in front of a virus-removal or ultrafiltration step. The criticality may not call for an integrity test being needed, as the next process step is the focal point to determine the quality of the product. In other cases, the 0.2 µm filter may be seen at a higher criticality level or might be specified to achieve a defined filtrate quality; at that point the risk assessment performed will guide the end-user to potentially integrity test such filter.

应由过滤器使用者自行决定是否测试用于降低生物负载的 0.2 µm 级过滤器的完整性。在某些情况下，过滤器用于保护另一个工艺步骤，或作为病毒去除或超滤步骤前的预过滤器。由于下一个工艺步骤是决定产品质量的关键点，这种关键程度可能不需要进行完整性测试。在其他情况下，0.2 微米过滤器可能处于更高的关键程度级别，或者可能为了达到规定的滤液质量而指定的；此时，进行的风险评估将指导最终用户对此类过滤器进行潜在的完整性测试。

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[1] For redundant sterilizing-filter systems, where the process has been validated as only requiring one filter, the redundant (typically first/upstream) filter does not have to be integrity-tested unless the primary sterilizing (typically second/downstream) filter fails its integrity test. However, if the redundant filtration system has been validated for the use of both filters to sterilize the product, then both filters must be integrity-tested.

对于冗余除菌过滤器系统，如果工艺经验证只需要一个过滤器，则冗余过滤器（通常是第一个/在上游）不必进行完整性测试，除非主除菌过滤器（通常是第二个/在下游）未能通过完整性测试。然而，如果冗余过滤系统经验证同时使用两个过滤器对产品进行灭菌，则必须对两个过滤器进行完整性测试

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Topic G: Sterilization – Steam Sterilizers

主题 G：灭菌-蒸汽灭菌器

Problem Statement
问题陈述

Are the European Standard EN 285:2015+A1:2021 and International Standard ISO 17665-1:2006 applicable to pharmaceutical autoclaves and automated-equipment steam-in-place (SIP)?
欧洲标准 EN 285:2015+A1:2021 和国际标准 ISO 17665-1:2006 是否适用于制药行业的高压灭菌器和自动化设备的在线蒸汽灭菌 (SIP)?

Recommendation
建议

Both EN 285 and ISO 17665-1 are valuable references that that have been developed to support the sterilization of medical devices used in healthcare but may be used to assess the construction, performance testing, operation, and/or validation of steam sterilizers and SIP systems in the pharmaceutical industry. However, neither standard has been officially adopted by regulatory authorities as GMP, nor has either standard been included in an FDA Guidance for Industry or similar guidelines as recommended best practice related to GMPs for pharmaceuticals.
EN 285 和 ISO 17665-1 都是很有价值的参考文献，它们是为支持医疗保健行业中使用的医疗器械灭菌而开发的，但也可用于评估制药行业中蒸汽灭菌器和 SIP 系统的建造、性能测试、操作和/或验证。然而，这两个标准均未被监管机构正式采纳为 GMP，也未被纳入 FDA 作为与药品 GMP 相关的最佳实践建议的行业指南或类似指南。

Rationale
理由

EN 285 *Sterilization – Steam sterilizers – Large sterilizers*, is a European Standard for adoption by member nations. It was revised and approved in 2015, with amendment A1 added in 2021. It applies specifically to the design, construction, and performance testing of large-steam sterilizers. Based upon the following statement contained within the Introduction, EN 285 is applicable to medical devices:
EN 285《灭菌-蒸汽灭菌器-大型灭菌器》是供成员国采用的欧洲标准。该标准于 2015 年修订并获得批准，并于 2021 年增加了 A1 修正案。它专门适用于大型蒸汽灭菌器的设计、建造和性能测试。根据引言中包含的以下声明，EN 285 适用于医疗器械：

> This document specifies test procedures and acceptance criteria to confirm whether the sterilizer is safe and can deliver an operating cycle for sterilizing the range of medical devices and loading configurations used in healthcare.
> 本文件规定了测试程序和验收标准，以确认灭菌器是否安全，并能提供一个操作循环，对医疗保健行业中使用的一系列医疗器械和装载配置进行灭菌。

Additionally, EN 285 provides the following reference to ISO 17665-1 and its applicability to validation and routine control of sterilization:
此外，EN 285 还对 ISO 17665-1 及其对灭菌验证和日常控制的适用性提供了如下引用：

…Requirements for the validation and routine control of sterilization are not addressed as they are specified EN ISO17665-1.
……由于 EN ISO17665-1 规定了灭菌的验证和日常控制要求，因此没有涉及这些要求。

In addition, Annex ZA to EN 285 relates various sections of the Standard as adequate to comply with EU Directive (EU) 2017/745 on medical devices (a steam sterilizer in this context being considered a medical device). However, it is clear from the text that EN 285 does not constitute the sole means of compliance with the Directive.
此外，EN 285 的附件 ZA 将该标准的各个章节（这些章节足以符合与欧盟指令（EU）2017/745 ）中关于医疗器械（蒸汽灭菌器在此情况下被视为医疗器械）的规定联系起来。不过，从文本中可以清楚地看出，EN 285 并不构成符合该指令的唯一途径。

ISO 17665-1:2006 Sterilization of Health Care Products—Moist Heat—Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices was published in 2006 and reaffirmed in 2013 prior to the latest version of EN 285. ISO 17665-1 includes EN 285 as a reference in the bibliography but does not include this document in its list of Normative References. Based on the title content of this document, it is applicable to medical devices.
ISO 17665-1:2006《医疗保健产品灭菌-湿热-第 1 部分：医疗器械灭菌工艺的开发、验证和日常控制要求》于 2006 年发布，并于 2013 年在 EN 285 最新版本之前得到重申。ISO 17665-1 将 EN 285 做为参考文献纳入参考目录，但未将该文件列入其规范性参考文献列表。根据该文件的标题内容，它适用于医疗器械。

ISO 17665-1 constitutes a consensus international standard and, if followed, may be considered to provide acceptable practice for the operation and validation of steam sterilizers for medical devices used in the healthcare industry. However, because this ISO standard has not been adopted and formally referenced within a published GMP regulation (such as ISO 14644, which is referenced in the 2022 revision of EU Annex 1), it does not constitute the sole means of compliance.
ISO 17665-1 是一项已达成共识的国际标准，如果遵照执行，可被视为为医疗保健行业使用的医疗器械蒸汽灭菌器的操作和验证提供了可接受的实践。然而，由于该 ISO 标准尚未在已公布的 GMP 法规（如欧盟附录 1 2022 年修订版中引用的 ISO 14644）中被采用及正式引用，因此它并不构成唯一的合规途径。

ISO/TS 17665-2:2009 Sterilization of health care products—Moist Heat—Part 2: Guidance on the ap- plication of ISO 17665-1 includes *Annex A: Evaluation of a sterilization process primarily based on the measurement of physical parameters*. This Annex aligns with EN 285 for sterilizer tests and performance requirements; however, it does allow that for sterilizers not complying with EN 285 “documented validation procedures could include tests and procedures from both this annex and Annex B.” In fact, portions of Annex A are directed more toward hospitals and medical practitioners (e.g., use of linens- based test packs) without the means for more sophisticated and definitive studies as required in the pharmaceutical industry.
ISO/TS 17665-2:2009《医疗保健产品灭菌-湿热灭菌-第 2 部分：ISO 17665-1 应用指南》包括《附录 A：主要基于物理参数测量的灭菌工艺评估》。该附录在灭菌器测试和性能要求方面的规定与 EN 285 一致；然而，对于不符合 EN 285 的灭菌器，该附录确实允许 "记录在案的验证程序可包括本附录和附录 B 中的测试和程序"。事实上，附录 A 的部分内容更多地针对医院和医疗从业人员（例如，使用亚麻布测试包），而没有采用制药行业所要求的更复杂、更明确的研究方法。

ISO 17665-2 Annex B: Evaluation of a sterilization process primarily based on biological inactivation and an accompanying mechanical air removal procedure incorporates biological indicator studies and is generally more aligned with pharmaceutical industry practices, as described in PDA TR-1. Most pharmaceutical practitioners would not accept the strictly physical measurements outlined in Annex A without biological-indicator data for confirmation. In any case, compliance with EN 285, while a valuable tool in evaluating sterilizer capability and performance, is not deemed to be a requirement to validate the sterilization processes used in pharmaceutical manufacturing.

ISO 17665-2 《附录 B：主要基于生物灭活和伴随的机械空气排除程序的灭菌工艺评估》包含了生物指标研究，通常更符合 PDA TR-1 中所述的制药行业实践。在没有生物指标数据可供确认的情况下，大多数制药从业人员都不会接受附件 A 中概述的严格物理测量方法。在任何情况下，符合 EN 285 标准虽然是评估灭菌器能力和性能的一个有价值的工具，但并不被视为验证药品生产中所用灭菌工艺的要求。

NOTE: Based on the titles of EN 285 and ISO 17665–1, neither standard is directly applicable to SIP systems, as SIP systems cannot be considered large sterilizers, nor are they used to directly sterilize medical devices.
注：根据 EN 285 和 ISO 17665-1 的标题，这两个标准都不能直接适用于 SIP 系统，因为 SIP 系统不能被视为大型灭菌器，也不能用于直接灭菌医疗器械。

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Topic H: Lyophilizer Leak Qualification

主题 H：冻干机泄露确认

Problem Statement
问题陈述
What is the frequency and the specification for the vacuum/leak integrity-testing of a lyophilizer?
冻干机真空/泄漏完整性测试的频率和标准是什么?

Recommendation
建议
The vacuum/leak integrity test should be performed after sterilization and prior to loading product for each batch. A leak rate may be conducted to assess the level of air infiltration caused by leaks. It may also be used to evaluate the integrity of the lyophilizer after steam sterilization. Such a test is referred to as a vacuum/leak integrity test to distinguish it from a true leak test. It is imperative to distinguish the difference in the tests and reported results.
真空/泄漏完整性测试应在灭菌后和每批产品装载前进行。泄漏率可用于评估泄漏造成的空气渗入程度。也可用于评估蒸汽灭菌后冻干机的完整性。这种测试被称为真空/泄漏完整性测试，以区别于真正的泄漏测试。在测试和报告结果中必须区分两者的差异。

A true leak rate—assessing the increase in the internal pressure of a lyophilizer starting from a low pressure (vacuum)—reflects the integrity of the system and the level of infiltration of air through connections to the chamber, condenser, and the chamber door. The measure value may be influenced by desorption of volatile components from the interior surfaces of the lyophilizer; this is referred to as outgassing.
真正的泄漏率--评估冻干机内部压力从低压（真空）开始的增加值--反映了系统的完整性以及通过连接到冻干室、冷凝器和冻干室门的空气渗入程度。测量值可能受到挥发性成分从冻干机内表面解吸的影响；这被称为漏气检测。

Though suitable values have been provided by equipment vendors, often as part of the equipment specifications, there has been no strong scientific evidence to substantiate what an acceptable value should be for vacuum/leak integrity test. The most important aspect for comparing results of multiple tests is reproducing the same conditions of temperature, pressure, and time, as they influence the results of the test.
虽然设备供应商已经提供了合适的数值，而且通常作为设备规范的一部分，但还没有强有力的科学证据来证明真空/泄漏完整性测试的可接受数值。比较多次测试结果最重要的方面是重现相同的温度、压力和时间条件，因为它们会影响测试结果。

Rationale
理由
The leak rate is useful to include it as part of the routine preventive maintenance and a test when changes or repairs are made. The in-process vacuum/leak integrity test is effective in ensuring that no leaks have developed from the expansion and contraction of the vessels during the steam sterilization and subsequent cooling. The condition of the equipment can have an influence on the results of the vacuum/leak integrity test. To assess the level of infiltration of the atmosphere through leaks without any contribution of outgassing,

the lyophilizer should be clean, dry, and empty and prepared to remove any volatile components. Results under these conditions more closely reflect a true loss of integrity of the sealing surfaces and elastomeric gaskets of the chamber, condenser connections, and the door. The value measured after steam sterilization is strongly influenced by the evolution of absorbed volatile components from the interior surfaces of the lyophilizer, yielding much different results than those of a true leak rate. The major component and contributor to a pressure increase is desorption of residual water upon completion of steam sterilization.
将泄漏率作为日常预防性维护的一部分以及进行更改或维修时的测试是有用的。工艺过程中的真空/泄漏完整性测试可有效确保在蒸汽灭菌和随后的冷却过程中，容器不会因膨胀和收缩而产生泄漏。设备的状况可能会对真空/泄漏完整性测试的结果产生影响。为了评估在没有任何排气作用的情况下通过泄漏渗透大气的程度，冻干机应清洁、干燥、排空的，并准备好去除所有的挥发性成分。在这些条件下测得的结果更能反映冻干室、冷凝器连接处和门的密封面和弹性垫圈的真实的完整性损失。蒸汽灭菌后测量的值会受到冻干机内表面吸收的挥发性成分逐渐增多的强烈影响，其结果与真实泄漏率的结果大不相同。压力增加的主要成因是蒸汽灭菌完成后残留水分的解吸。

Values may be reported as a pressure increase over time, such as microns (millitorr) per minute, or μmHg per minute, or as microns (millitorr) per volume–time. Expressing results are suitable for trending results for the same size lyophilizer. Including the volume factor is useful for comparing the results for different sizes of lyophilizers.
数值可报告为压力随时间的增加值，如每分钟微米（毫托）或每分钟 μmHg，或每体积-时间微米（毫托）。用这种方法表示的结果适用于对相同尺寸冻干机的结果进行趋势分析。加入体积系数则有助于比较不同尺寸冻干机的结果。

Assuring the integrity of the lyophilizer, such that the infiltration of air that is of unknown and un- controlled microbiological and chemical quality, leads to a higher level of confidence in the product quality. As the product in the lyophilizer is unsealed and no longer protected by unidirectional air that has been HEPA-filtered, it is the integrity of the lyophilizer that protects the product from potential contamination. As such, it is important to verify that there is adequate integrity prior to placing product in the lyophilizer.
确保冻干机的完整性，防止未知和未受控的微生物和化学物质的空气渗入，从而提高产品质量的可信度。由于冻干机中的产品是非密封的，不再受到经过高效空气过滤器过滤的单向空气的保护，因此正是冻干机的完整性保护产品免受潜在污染。因此，在将产品放入冻干机之前，必须验证冻干机具有足够的完整性。

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Topic I: Sterilizing Grade Gas or Vent Filter Integrity Testing

主题 I：气体除菌过滤器或通气过滤器完整性测试

Problem Statement
问题陈述
How often should sterilizing gas or vent filters be verified for integrity?
应多久检查一次气体除菌过滤器或通气过滤器的完整性？

Recommendation
建议
Assurance of microbial retention throughout the critical filtration process should be confirmed by a post-filtration integrity test.
应通过过滤后完整性测试来确保微生物在整个关键过滤过程中的截留。

As a general rule, a sterilizing gas filter (hydrophobic) should be integrity-tested prior to being placed into a critical application to ensure that it is capable of performing its stated function. For critical sterile applications (product or critical surface-contact), the best practice is to test filters upon installation or in situ, and after use. For gas filters in extended-use applications, or in less stringent applications, some filter users have specified an integrity-test frequency based on factors such as historical process durability, time online, or number of sterilization cycles. No single approach applies to all applications, and an appropriate testing frequency and rationale should be selected using risk analysis considering the impact on product quality.
一般来说，气体除菌过滤器（疏水性）在投入关键应用之前应进行完整性测试，以确保其能够执行既定的功能。对于关键灭菌应用（产品或关键表面接触），最佳实践是在安装时、或在线以及使用后对过滤器进行测试。对于长期使用的气体过滤器或要求不那么严格的应用，一些过滤器用户会根据历史工艺耐久性、在线时间或灭菌周期数等因素来规定完整性测试频率。没有一种单一的方法适用于所有应用，应在考虑到对产品质量影响的情况下，通过风险分析来选择合适的测试频率和理由。

A risk-based approach to integrity-testing should be used for sterilizing-grade filters in nonsterile applications.
对于非无菌应用中的除菌级过滤器，应采用基于风险的完整性测试方法。

Rationale
理由
The risk associated with some of these practices is that any product produced since the last successful integrity test may not meet the expected microbial quality attributes if the filter fails to meet the required test criteria. This, in turn, will trigger the need for thorough investigation and may result in a loss of product. In these cases, more frequent testing may be more appropriate.
其中一些做法的风险在于，如果过滤器未能满足所需的测试标准，那么自上次完整性测试成功以来生产的任何产品都可能不符合预期的微生物质量属性。结果，这就需要进行彻底调查，并可能导致产品损失。在这种情况下，更频繁的检测可能更为合适。

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Topic J: Pre-Use, Post-Sterilization Integrity Test of Sterilizing Filters

主题 J: 除菌过滤器使用前和灭菌后的完整性测试

Problem Statement
问题陈述

Should a pre-use, post-sterilization integrity test (PUPSIT) of sterilizing filters be performed?
是否应该对除菌过滤器进行使用前、灭菌后完整性测试（PUPSIT）？

Recommendation
建议

The current version (2022) of the EU Annex 1 requires the performance of a pre-use, post sterilization integrity test, where possible. Specifically, "the integrity of the sterilized filter assembly should be verified by integrity testing before use, to check for damage and loss of integrity caused by the filter preparation prior to use."
欧盟附录 1 的当前版本（2022 ）要求尽可能进行使用前和灭菌后的完整性测试。具体来说，"除菌过滤器组件的完整性应通过使用前的完整性测试来验证，以检查使用前的过滤器装置是否造成损坏和完整性丧失"。

It is however recognized that "pre-use post sterilization integrity testing (PUPSIT) may not always be possible after sterilization due to process constraints (e.g., the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of non-sterility." (EU Annex 1)
然而，人们认识到，"由于工艺上的限制（如过滤极少量的溶液），灭菌后并不总能进行使用前灭菌后完整性测试（PUPSIT）。在这种情况下，可以采取另一种方法，前提是已经进行了彻底的风险评估，并通过实施适当的控制措施来降低任何非无菌风险，从而达到合规要求"。(欧盟附录 1)

The PUPSIT of liquid sterilizing-grade filters as a means to ensure a filter's integrity throughout its use should be evaluated on a case-by-case basis by a comprehensive risk assessment.
液体除菌过滤器的 PUPSIT 作为确保过滤器在整个使用过程中的完整性的一种手段，应根据具体情况逐一进行全面的风险评估。

It is essential that the PUPSIT process and assembly be designed so that it does not pose an unacceptable level of risk to sterile product. A risk assessment should be used to identify product quality risks and controls of the current process and, if required, to mitigate those risks.
PUPSIT 工艺和装配的设计必须确保不会对无菌产品造成不可接受的风险。应通过风险评估来确定产品质量风险和当前工艺的控制措施，并在必要时降低这些风险。

Where a risk assessment is used to determine product-quality risk associated with the filtration process and the use of the PUPSIT, the risk assessment should be executed by line and by product to include a side-by-side comparison of control measures that may include conducting versus not conducting the PUPSIT. The risk assessment should evaluate product and process characteristics and establish the most appropriate controls for the process. The risk assessment should be performed in an unbiased manner and must not have predetermined outcomes.

如果使用风险评估来确定与过滤工艺和使用 PUPSIT 相关的产品质量风险，则应按生产线和产品执行风险评估，包括并行比较控制措施，其中可能包括进行与不进行 PUPSIT。风险评估应评估产品和流程特性，并为流程制定最合适的控制措施。风险评估应以无偏见的方式进行，不得预先确定结果。

The risk assessment should include risk-related elements, such as the following:
风险评估应包括与风险有关的内容，如以下内容：

- Effect of a filter failure, should one occur, including the potential introduction of nonsterile product into an aseptic area
  过滤器一旦发生故障造成的影响，包括可能将非无菌产品带入无菌区域
- Risk of contamination due to additional manipulations on presterilized filters (e.g., ready-to-use filters)
  由于对预灭菌过滤器（如即用型过滤器）进行额外操作而产生的污染风险
- Ability to detect a potential breach
  检测潜在漏洞的能力
- Likelihood of microbial ingress to the downstream side of the filter (when a PUPSIT is performed)
  微生物进入过滤器下游侧的可能性（进行 PUPSIT 时）
- Potential for blocking the sterilizing filters due to the processing stream (particulate or bioburden)
  由于工艺流程（微粒或生物负载）而堵塞消毒过滤器的可能性
- Whether the existing production lines can be modified to add the ability to perform a PUPSIT and assess the potential risk to the product or sterile boundary by implementing such modifications
  是否可以对现有生产线进行改造，以增加执行 PUPSIT 的能力，并评估通过实施此类改造对产品或无菌边界造成的潜在风险
- Whether there is a CCS in place for the steam-sterilization process (e.g., SIP) to prevent filter damage during SIP
  蒸汽灭菌过程（如 SIP）是否有 CCS，以防止过滤器在 SIP 过程中损坏
- Impact of wetting fluid on product dilution and product attributes
  润湿剂对产品稀释和产品属性的影响
- Impact of the additional time required on time-sensitive processes
  所需额外时间对时间敏感流程的影响

The interventions and manipulations associated with the assembly and performance of PUPSIT should be included in the APS program, including those performed in the Grade A environment and those performed outside of the Grade A area that are assessed to pose a risk to the aseptic process.
与 PUPSIT 组装和操作相关的干预和操作应纳入 APS 计划，包括在 A 级环境中进行的干预和操作，以及在 A 级区域外进行的、经评估可能对无菌工艺构成风险的干预和操作。

NOTE: PUPSIT is not required for filtration of sterilized product-contact gases, as it is expected that a gas does not have the properties to mask any eventual damage in the filter membrane.
注：PUPSIT 不需要用于过滤已灭菌的与产品接触的气体，因为预计气体不具有掩盖滤膜的任何最终损坏的特性。

Rationale
理由

The prior recommendation by PDA for PUPSIT was with reference to a risk-based assessment and with due

consideration of existing processes for which the introduction of PUPSIT may otherwise result in a higher risk profile by virtue of required manipulations. PDA recognizes that PUPSIT is an expectation of European Union and PIC/S regulators. Therefore, PDA is noting and recommending that PUPSIT be implemented in- line with evolving regulatory expectations and on the basis of a well- designed implementation.
PDA 先前对 PUPSIT 的建议是参考基于风险的评估，并适当考虑了现有流程，对于这些流程而言，引入 PUPSIT 可能会由于所需的操作而导致更高的风险。PDA 认识到 PUPSIT 是欧盟和 PIC/S 监管机构的期望。因此，PDA 注意到并建议，PUPSIT 的实施应符合不断发展的监管期望，并以精心设计的实施为基础。

If a well-designed PUPSIT procedure is assessed to show that the use of PUPSIT does not result in increased risk, then the risk of PUPSIT should not outweigh its benefit. Provisions can be made, how- ever, for processes for which the undertaking of PUPSIT is not supported, for example, in the case of small volumes. These provisions include a comprehensive risk assessment for which an alternative to PUPSIT may be rationalized and for which the controls in place must be capable of detecting a nonintegral filter.
如果对设计良好的 PUPSIT 程序进行评估，表明使用 PUPSIT 不会增加风险，那么 PUPSIT 的风险不应超过其益处。不过，可以对不支持 PUPSIT 的过程做出规定，例如，在小批量的情况下。这些规定包括一项全面的风险评估，可以合理化 PUPSIT 的替代方案，并且现有的控制措施必须能够检测到不完整的过滤器。

Whereas a PUPSIT could provide added assurance of a filter's integrity throughout processing and re- duce the risk of product loss, the risk of implementation of such a test must be assessed for each process and manufacturing site. A PUPSIT procedure may result in a higher risk to product quality, especially where activities are performed in the Grade A area and may involve exposure of open connections. Integrity tests of filters after sterilization and pre-use, in many cases, may increase the actual risk of product contamination due to downstream manipulations and/or the addition of equipment into the downstream process. This contamination might not be detected afterward; therefore, it is important to perform or simulate these activities during the APS.
虽然 PUPSIT 可以进一步保证过滤器在整个加工过程中的完整性，并降低产品损失的风险，但必须对每个工艺和生产场所进行风险评估。PUPSIT 程序可能会导致更高的产品质量风险，特别是在 A 级区域进行的活动，可能会暴露开放式连接。在灭菌和使用前对过滤器进行完整性测试，在许多情况下，可能会增加因下游操作和/或在下游工艺中添加设备而造成产品污染的实际风险。这种污染事后可能无法检测到；因此，在 APS 期间执行或模拟这些活动非常重要。

A PUPSIT may provide the opportunity to detect nonintegral filters after sterilization and prior to use, thus preventing potential product loss (in case refiltration is not possible) and preventing the introduction of contamination into an aseptic area.
PUPSIT 提供了在灭菌后和使用前检测出非完整过滤器的机会，从而防止潜在的产品损失（在无法再过滤的情况下），并防止污染进入无菌区。

The use of PUPSIT, in part, is based on concerns related to the potential masking of a nonintegral filter by product or product debris. Since the risk of masking depends on the characteristics of the product, these characteristics could provide valuable information to be used in support of the PUPSIT design.
PUPSIT 的使用在一定程度上是基于对产品或产品碎片可能掩盖非完整过滤器的担忧。由于掩蔽的风险取决于产品的特性，这些特性可以提供有价值的信息，用于支持 PUPSIT 设计。

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Topic K: Integrity Testing of Sterilizing Filters

主题 K: 除菌过滤器的完整性测试

Problem Statement
问题陈述

What is the maximum number of times that a post-use integrity test of a sterilizing filter should be performed in case of initial failure?
如果除菌过滤器出现初始故障，最多应进行多少次使用后完整性测试？

Recommendation
建议

The current recommendation in PDA *Technical Report No. 26: Sterilizing Filtration of Liquids* includes a detailed process including up to three tests at the filter-user site. After a filter has failed three times at the user site, submitting the filter to the filter manufacturer for further investigation and testing is recommended.
*PDA 第 26 号技术报告：液体除菌过滤*中的现行建议包括一个详细的过程，其中包括在过滤器用户现场进行多达三次的测试。当过滤器在用户现场经过三次测试失败后，建议将过滤器提交给过滤器制造商进行进一步的调查和测试。

The integrity of the filter assembly and connections to the integrity tester should be checked prior to each integrity test.
在每次完整性测试之前，应检查过滤器组件和与完整性测试仪连接的完整性。

Rationale
理由

After initial failure, the tests are performed in a progressive and corrective manner to determine whether the integrity test result is a false failure or true failure. Most filter failures are the result of improper wetting of the entire filter membrane matrix. This happens for a multitude of reasons, for example, product residues, temperature fluctuations, and pressure conditions during flushing. Rewetting and checking the filtration system for leaks can remedy the false failure. If the filter fails a second time, it commonly is recommended to flush a liquid filter with a lower surface-tension fluid like water or a solvent mixture to determine whether wetting problems are the issue.
初次失效后，将以渐进和纠正的方式进行测试，以确定完整性测试结果是假失效还是真失效。大多数过滤器故障都是由于整个滤膜基质湿润不当造成的。发生这种情况的原因很多，例如产品残留、温度波动和冲洗时的压力条件。重新润湿和检查过滤系统是否有泄漏可以纠正错误故障。如果过滤器再次出现故障，通常建议用水或混合溶剂等表面张力较低的流体冲洗液体过滤器，以确定是否存在润湿问题。

If the filter fails a third time at the filter-user site, submitting the filter to the filter manufacturer for thorough investigations is advisable as they have the expertise, tools, and means to provide supporting information for the investigation to determine whether the filter-integrity test failure is a true failure and why the failure may have happened. It is important to determine the root cause of the filter failure to avoid future filter failure or filter damage.
如果过滤器在用户现场第三次出现故障，建议将过滤器提交给过滤器制造商进行彻底调查，因为制造商拥

有专业技术、工具和手段，可以为调查提供支持信息，以确定过滤器完整性测试故障是否属实，以及故障发生的原因。重要的是要确定过滤器故障的根本原因，以避免今后出现过滤器故障或过滤器损坏。

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Topic L: Use of Two Sterilizing-Grade Filters for Product Sterile Filtration

主题 L: 使用两个除菌级过滤器进行产品除菌过滤

Problem Statement
问题陈述
Should redundant (in-series) sterilizing filters be used and, if so, where should the filters be located?
是否应使用冗余（串联）除菌过滤器?

Recommendation
建议
The use of redundant, or two sterilizing-grade filters in series should not be required. A company may make a risk-based decision to include a second sterilizing filter in a series.
可以不使用冗余的或两个串联的除菌过滤器。公司可能会做出基于风险的决定，在系列中加入第二个除菌过滤器。

The use of filters in parallel is not redundant filtration and may be qualified to be used in specific circumstances.
并联使用过滤器并不是冗余过滤，在特定情况下可以使用。

The final sterilizing filter should be physically located to minimize the number of aseptic connections that occur after filtration of the product.
最终除菌过滤器的物理位置应尽量减少产品过滤后的无菌连接次数。

The final sterilizing filter should be positioned as close to the point of fill as possible, provided the positioning of that filter does not adversely affect the performance of aseptic processing activities or pose an increased risk of contamination to the sterile product.
最终除菌过滤器的位置应尽可能靠近灌装点，前提是该过滤器的位置不会对无菌生产活动产生不利影响或增加无菌产品受污染的风险。

Where redundant filters are used and PUPSIT is performed, considerations should be used to perform PUPSIT on the filter considered to be the product sterilizing filter.
在使用冗余过滤器和执行 PUPSIT 时，应考虑在被视为产品除菌过滤器的过滤器上执行 PUPSIT。

Rationale
理由
A single set of sterilizing-grade filters that are appropriately selected, sized, validated, and operated within the validated parameters should be adequate to sterilize products with proper bioburden control. Therefore, a redundant filter system should not be needed to further reduce the risk of inadequate sterilization and may add unnecessary interventions.
单套除菌过滤器经过适当选择、尺寸确定、验证并在验证参数范围内运行，应足以在适当控制生物负载的情况下对产品进行除菌。因此，不需要冗余的过滤器系统来进一步降低灭菌不充分的风险，而且可能会增加不必要的干预。

When product loss due to possible post-use filter-integrity failure is an unacceptable risk, redundant filtration could be considered as a business decision. In that situation, both filters should be located as close as possible to the filling operation. At least one of the two filters must demonstrate integrity for the sterilization to be considered successful. However, it must be clear in the appropriate documentation (e.g., CCS, chemistry, manufacturing, and controls section, or master validation plan) how such a process is to be managed.
当过滤器使用后可能出现的完整性故障导致产品损失的风险无法接受时，可以考虑使用冗余过滤。在这种情况下，两个过滤器应尽可能靠近灌装操作。两个过滤器中至少有一个必须证明完整性，除菌才算成功。不过，在适当的文件（如 CCS、化学、制造和控制部分或主验证计划）中必须明确如何管理此类过程。

In situations where parallel filtration is required (e.g., increasing filtration surface area without increasing filter length), use of two or more smaller filters in parallel could be considered. However, this is not redundant filtration, and all filters must meet all requirements, including the integrity requirement.
在需要并联过滤的情况下（例如，在不增加过滤器长度的情况下增加过滤表面积），可以考虑并联使用两个或多个较小的过滤器。不过，这并不是冗余过滤，所有过滤器都必须满足所有要求，包括完整性要求。

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VII. Critical Utilities 关键公用设施

Topic A: Methods of Production Requirements for Water for Injection

主题 A: 注射用水的生产方法要求

Problem Statement
问题陈述
What methods of production for WFI should be employed?
应采用何种方法生产 WFI?

Recommendation
建议
WFI must meet pharmacopeial requirements for purity. Any method that has been validated to reliably yield and maintain water in compliance with the relevant pharmacopeial standard may be employed.
WFI 必须符合药典对纯度的要求。可以采用任何经过验证的方法，可靠地生产和保持符合相关药典标准的水。

Distillation is a method referred to by European regulatory agencies; alternative methods, such as reverse osmosis in combination with other purification methods, are appropriate if the quality of WFI is shown to be equivalent.
蒸馏法是欧洲监管机构提到的一种方法；如果证明 WFI 的质量相当，也可以采用其他方法，如结合其他净化方法的反渗透法。

Proper design, control, and monitoring should be implemented and should include both the production and distribution systems to ensure continuous assurance of the quality of the output and prevention of distribution system biofilm.
应实施适当的设计、控制和监测，并应包括制备和分配系统，以确保持续保证注射用水输出的质量和预防分配系统生物膜的产生。

Levels of control and monitoring should be based on a risk assessment of the specific WFI production process and equipment capabilities.
控制和监测水平应基于对特定 WFI 生产工艺和设备能力的风险评估。

Rationale
理由
Flexibility in selection of technologies that can provide the required quality of water will permit the adoption of the best methodologies as more advanced systems become available.
灵活选择可提供所需水质的技术，将有助于在有更先进的系统时采用最佳方法。

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Topic B: Requirements for Water for Injection

主题 B: 对注射用水的要求

Problem Statement
问题陈述
What are the requirements for preventing microbial contamination of WFI?
防止 WFI 微生物污染的要求是什么?

Recommendation
建议
Production of WFI should be via distillation or other equally effective, qualified technology or combinations of qualified technologies. Maintenance of WFI quality may be achieved via a continuously recirculating system that operates at an elevated temperature. Hot recirculating systems operating at lower temperatures, or even ambient or cold loops, are acceptable but should have a method to ensure that the bioburden of the WFI remains under control. This may also be achieved through periodic sanitization (e.g., through hot water recirculation or periodic steaming of empty loop and vessel) during periods of non-use. WFI systems should be tested according to the requirements of the applicable pharmacopeia to demonstrate control.
应通过蒸馏或其他同样有效的合格技术或合格技术的组合来生产 WFI。可通过在高温下运行的连续再循环系统来保持 WFI 的质量。在较低温度下运行的热循环系统，甚至是常温或冷循环系统也是可以接受的，但应采用一种方法来确保 WFI 的生物负载始终处于受控状态。在不使用期间，也可以通过定期消毒（例如，通过热水循环或定期性对空环路和容器进行蒸汽处理）来实现这一目标。应根据适用药典的要求对 WFI 系统进行测试，以证明其控制能力。

Dead legs in the design and installation of the WFI distribution system and points of connection should be avoided. Special consideration should be given, and steps taken, to prevent microbiological contamination and biofilm formation, where user-point connections result in spaces where standing water and/or moisture can accumulate.
应避免在设计和安装 WFI 分配系统和连接点时出现死角。如因用户连接点导致空间积水和/或潮气，则应特别考虑并采取措施防止微生物污染和生物膜的形成。

Rationale
理由
Contact of WFI at elevated temperatures (e.g., >70 °C) should be sufficient to maintain the WFI distribution system in a quality state. However, a well-designed system can be validated to maintain acceptable quality at lower temperatures. A system designed to operate at ambient temperatures (e.g.,<70 °C) requires periodic sanitization with hot water or steam. Steam should not be used when water systems are not designed to vent steam. Systems that are able to be pressurized and are properly de- signed may use steam.
WFI 在高温（如 >70 °C）下足以使 WFI 分配系统保持优质状态。不过，经验证的设计良好的系统可以在较低温度下保持可接受的质量。设计在环境温度下运行的系统（如<70 °C）需要定期用热水或蒸汽消毒。如果供水系统的设计不能排出蒸汽，则不应使用蒸汽。可以加压并经过适当消毒的系统可以使用蒸汽。

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