Guidance for Industry

Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

行业指南
无菌加工生产的无菌药品
—现行的生产质量管理规范(cGMP）

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

September 2004
Pharmaceutical CGMPs

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Guidance for Industry[1]
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I. INTRODUCTION
简介

This guidance is intended to help manufacturers meet the requirements in the Agency's current good manufacturing practice (CGMP) regulations (2l CFR parts 210 and 211) when manufacturing sterile drug and biological products using aseptic processing. This guidance replaces the 1987 *Industry Guideline on Sterile Drug Products Produced by Aseptic Processing (Aseptic Processing Guideline)*. This revision updates and clarifies the 1987 guidance.

本指南旨在帮助生产商在应用无菌工艺制造无菌药品和生物制剂时，达到 FDA cGMP 规章(美国联邦法规的第 210 及第 211 节)要求。本指南替代 1987 年《通过无菌加工生产无菌药品的行业指南(无菌工艺指南)》。本修订版本对 1987 年的指南进行更新和澄清。

For sterile drug products subject to a new or abbreviated drug application (NDA or ANDA) or a biologic license application (BLA), this guidance document should be read in conjunction with the guidance on the content of sterile drug applications entitled *Guideline for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (Submission Guidance). The Submission Guidance describes the types of

[1] This guidance was developed by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Office of Regulatory Affairs (ORA).

[1] 本指南由药品评价及研究中心(CDER)与生物制品评价及研究中心(CBER)和法规事务办公室合作编制。

information and data that should be included in drug applications to demonstrate the efficacy of a manufacturer's sterilization process. This guidance compliments the Submission Guidance by describing procedures and practices that will help enable a sterile drug manufacturing facility to meet CGMP requirements relating, for example, to facility design, equipment suitability, process validation, and quality control.

作为新药申请(NDA)、简化新药申请(ANDA)或生物制品注册申请（BLA）主题的无菌药物，除本指南外，还应结合 <<人用药品和兽药申请中提交灭菌工艺验证文件的指南（提交指南）>> 中关于无菌药品申请的内容。此<<提交指南>>描述了在药品申请中应包括的能证明厂家灭菌工艺功效的信息和数据。本指南作为<<提交指南>>的补充，所描述的步骤和操作将有助于无菌药品生产工厂达到 cGMP 关于，例如，厂房设计、设备适用性、工艺验证和质量管理控制等等的要求。

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

包括本指南在内，FDA 的各项指南文件在法律上无强制效力。除非引用特定的法规规定，否则各项指南仅描述 FDA 现在就此主题的想法和意见，并且应当被视为建议。在 FDA 的指南中，“应该”这个词意味着建议和推荐，而不是必须。

The text boxes included in this guidance include specific sections of parts 210 and 211 of the Code of Federal Regulations (CFR), which address current good manufacturing practice for drugs. The intent of including these quotes in the text boxes is to aid the reader by providing a portion of an applicable regulation being addressed in the guidance. The quotes included in the text boxes are not intended to be exhaustive. Readers of this document should reference the complete CFR to ensure that they have complied, in full, with all relevant sections of the regulations.

本指南中的文本框引用美国联邦法规(CFR)的第 210 及第 211 节关于药物 CGMP 的相关法令，其目的是为读者提供帮助，而并不是打算无所遗漏。读者应该参考完整的美国联邦法规 (CFR)，确保完全遵守所述法规的所有相关部分。

II. BACKGROUND
背景

This section describes briefly both the regulatory and technical reasons why the Agency is developing this guidance document.

本章简要描述 FDA 开发本行业指南的法规原因和技术原因。

A. Regulatory Framework
法规架构

This guidance pertains to current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211) when manufacturing sterile drug and biological products using aseptic processing. Although the focus of this guidance is on CGMPs in 21 CFR 210 and 211, supplementary requirements for biological products are in 21 CFR 600-680. For biological products regulated under 21 CFR parts 600 through 680, §§210.2(a) and 211.1(b) provide that where it is impossible to comply with the applicable regulations in both parts 600 through 680 and parts 210 and 211, the regulation specifically applicable to the drug product in question shall supercede the more general regulations.

本指南符合使用无菌加工生产无菌药品和生物制品过程中的 cGMP 法规要求（21 CFR 210 及 211 节）。此指南的重点是 21 CFR 210 及 211 节内的 cGMP 要求， 生物制品的补充要求见 21 CFR 600 - 680 节。 对于受 21 CFR 600 - 680 节管制的生物制品，§§210.2(a)和 211.1(b)规定：在无法同时符合 600 – 680 节和 210 及 211 节相关要求的情况下，适用于所述药品的具体规定应当代替一般性规定。

B. Technical Framework
技术架构

There are basic differences between the production of sterile drug products using aseptic processing and production using terminal sterilization.

在使用无菌加工生产的无菌药品生产与使用最终灭菌生产的无菌药品生产之间，有根本性的区别。

Terminal sterilization usually involves filling and sealing product containers under high-quality environmental conditions. Products are filled and sealed in this type of environment to minimize the microbial and particulate content of the in-process product and to help ensure that the subsequent sterilization process is successful. In most cases, the product, container, and closure have low bioburden, but they are not sterile. The product in its final container is then subjected to a sterilization process such as heat or irradiation.

最终灭菌通常涉及在高质量环境条件下分装和封口产品容器。在这种类型环境下分装和封口产品，以最小化中间产品内的微生物和颗粒含量，并帮助确保随后的灭菌工艺成功。在大多数情况下，产品、容器和密封的生物负载低，但并非无菌。在最终容器内的产品随后进入灭菌工艺，例如加热或放射灭菌。

In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together.[2] Because there is no process to

[2] Due to their nature, certain products are aseptically processed at an earlier stage in the process, or in their entirety. Cellular therapy products are an example. All components and excipients for these products are rendered sterile, and release of the final product is contingent on determination of sterility. See Appendix III.

[2] 根据药品的性质，有些药品在加工的更早阶段或在整个生产过程中采用无菌操作。细胞疗法产品就是例子。这些药品的所有成分和赋形剂都应当是无菌的，成品上市根据无菌性测定而决定。参考附录 III。

sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment. Aseptic processing involves more variables than terminal sterilization. Before aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes. For example, glass containers are subjected to dry heat; rubber closures are subjected to moist heat; and liquid dosage forms are subjected to filtration. Each of these manufacturing processes requires validation and control. Each process could introduce an error that ultimately could lead to the distribution of a contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control. A terminally sterilized drug product, on the other hand, undergoes final sterilization in a sealed container, thus limiting the possibility of error.[3]

在无菌加工中, 药品、容器和密封首先分别使用合适方法灭菌，然后组合到一起。[2]由于没有在最终容器内灭菌药品的工艺，因此在特别高质量的环境中分装和封口容器是非常关键的。无菌加工涉及的变量比最终灭菌更多。在无菌组装成最终产品之前，最终产品的各个组成部分通常进入不同的灭菌工艺。比如：玻璃容器进行干热灭菌 ,橡胶密封进行蒸汽灭菌，液体剂型则进行过滤。每个生产工艺都需要验证及控制。每个过程都有可能出现误差，从而最终导致污染药品上市。在无菌装配之前或期间，已灭菌药品、成分、容器或密封的任何手工或机器操作都有污染的风险，因此需要加以仔细控制。而最终灭菌的药品在密封容器中进行最终灭菌，因此限制了出错的可能。[3]

Sterile drug manufacturers should have a keen awareness of the public health implications of distributing a nonsterile product. Poor CGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient.

无菌药品生产商应该清楚地认识到销售非无菌药品所造成的公众安全影响。生产设施的劣质 cGMP 条件可能最终给患者带来危及生命的风险。

III. SCOPE
适用范围

This guidance document discusses selected issues and does not address all aspects of aseptic processing. For example, the guidance addresses primarily finished drug product CGMP issues while only limited information is provided regarding upstream bulk processing steps. This guidance updates the 1987 Aseptic Processing Guideline primarily with respect to personnel qualification, cleanroom design, process design, quality control, environmental monitoring, and review of production records. The use of isolators for aseptic processing is also discussed.

[3] Nearly all drugs recalled due to nonsterility or lack of sterility assurance in the period spanning 1980-2000 were produced via aseptic processing.

[3]在 1980-2000 年期间，几乎所有由于无菌性受到破坏或缺乏无菌性保证而召回的药品，都是通过无菌工艺生产的。

本指南只涉及选定问题，未涉及无菌加工的全部范畴。例如：此指南主要针对成品 cGMP 内容，而上游的半成品加工步骤只有部分信息。本指南是 1987 年《无菌加工指南》的更新版本，主要修订方面是人员资质、洁净室设计、工艺设计、质量控制、环境监测及生产记录审核。讨论在无菌加工中无菌隔离系统的使用。

Although this guidance document discusses CGMP issues relating to the sterilization of components, containers, and closures, terminal sterilization of drug products is not addressed. It is a well-accepted principle that sterile drugs should be manufactured using aseptic processing only when terminal sterilization is not feasible. However, some final packaging may afford some unique and substantial advantage (e.g., some dual-chamber syringes) that would not be possible if terminal sterilization were employed. In such cases, a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility assurance.

虽然本指南讨论与成分、容器和密封灭菌有关的 cGMP 事宜，但并未涉及药品的最终灭菌。只有在最终灭菌不可行的情况下，才使用无菌加工生产无菌药品，这是一个众所周知的原则。然而，一些最终包装可以提供独特和切实的好处（如一些双室注射器），但这些最终包装不能使用最终灭菌的 。在这种情况下，生产商可以考虑增加工艺步骤，以增加无菌保证水平。

A list of references that may be of value to the reader is included at the conclusion of this document.

本指南结尾列出参考文献，读者可以借鉴。

IV. BUILDINGS AND FACILITIES
厂房和建筑

21 CFR 211.42(b) states, in part, that "The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination."

CFR211.42(b)规定，"药物成分、容器、密封、标签、中间材料和药品在厂房内或厂房间的运输应该能够防止污染。"

21 CFR 211.42(c) states, in part, that "Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures: * * * (10) Aseptic processing, which includes as appropriate: (i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable; (ii) Temperature and humidity controls; (iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar; (iv) A system for monitoring environmental conditions; (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions; (vi) A system for maintaining any equipment used to control the aseptic conditions."

CFR211.42(c)规定，"操作应当在有充足空间的指定区域内进行。操作应该分隔或指定的区域，或者有其它控制系统，以便在下面过程中防止污染或混淆： …（10）无菌加工，措施包括以下：(i)地面、墙面和天花板的表面平滑、坚硬并且容易清洁；(ii)温度和湿度控制；(iii)供应通过 HEPA 滤器过滤的空气，并保持正压，不论气流是层流或非层流；(iv)检测环境质量的系统；(v)清洁及消毒房间和设备以产生无菌条件的系统；(vi) 维护用于控制无菌环境的任何设备的系统。"

21 CFR 211.46(b) states that "Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product."

CFR211.46(b)规定，"当对生产、制造、包装或储存药品有利时，应当提供能充分控制压差、微生物、尘埃粒子、湿度及温度的设备。"

21 CFR 211.46(c) states, in part, that "Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas * * *."

CFR211.46(c)规定，"当对供应生产区域的空气有利时，应当提供空气过滤系统，包括初效过滤器及颗粒空气过滤器…。"

21 CFR 211.63 states that "Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance."

CFR211.63 规定，"用于生产、加工、包装及储存药品的设备应当设计合理，有足够空间并且被适当定位，以方便其既定用途的操作并且方便清洁和维护。"

21 CFR 211.65(a) states that "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

CFR211.65(a)规定，"设备接触药品成分、中间材料或药品的表面应该无反应、无添加并且无吸附，不会改变药品的安全性、成分、浓度、质量或纯度并使它们超出官方或已经建立的标准。"

21 CFR 211.67(a) states that "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

CFR211.67(a)规定，"设备和器具应当以合适间隔清洁、维护和消毒，以预防故障或污染改变药品的安全性、成分、浓度、质量或纯度并使它们超出官方或已经建立的标准。"

21 CFR 211.113(b) states that "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."

CFR211.63(b)规定，"应当建立及遵从预防无菌药品受到微生物感染的合适书面程序。 这些程序应当包括任何灭菌工艺的验证。"

As provided for in the regulations, separate or defined areas of operation in an aseptic processing facility should be appropriately controlled to attain different degrees of air quality depending on the nature of the operation. Design of a given area involves satisfying microbiological and particle criteria as defined by the equipment, components, and products exposed, as well as the operational activities conducted in the area.

如法规规定，无菌加工设施中操作的分隔或指定区域应当受到合理控制，以根据操作的性质而获得空气质量的不同水平。给定区域的设计应该满足微生物和尘埃粒子标准，所述标准根据设备、成分和暴露的产品以及在该区域内进行的操作而确定。

Clean area control parameters should be supported by microbiological and particle data obtained during qualification studies. Initial cleanroom qualification includes, in part, an assessment of air quality under as-built, static conditions. It is important for area qualification and classification to place most emphasis on data generated under dynamic conditions (i.e., with personnel present, equipment in place, and operations ongoing). An adequate aseptic processing facility monitoring program also will assess conformance with specified clean area classifications under dynamic conditions on a routine basis.

洁净区域控制参数应当得到验证期间获得的微生物和尘埃粒子数据支持。洁净室的首次验证其中包括对空态、静态条件下空气质量的评价。区域验证和分级中，重要的是将大部分重点放在动态条件（即设备到位、人员到岗并且进行操作）下产生的数据。充分的无菌加工设施监测程序也将评估在日常运作的动态条件下与特定洁净区域分级的符合性。

The following table summarizes clean area air classifications and recommended action levels of microbiological quality (Ref. 1).

下表总结了洁净区域空气分级以及推荐的微生物指标的行动限（参考文献 1）。

TABLE 1- Air Classifications[a]
表 1 – 空气洁净级别 [a]

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
洁净区域级别（0.5 um 颗粒/ ft^3）	ISO 级别 [b]	≥0.5 µm 颗粒/ m^3	浮游菌行动限 [c]（cfu/m^3）	沉降菌行动限 [c,d] (直径 90mm 平板；cfu/4 小时)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

a- All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
所有级别划分都基于动态下暴露的材料 / 物品附近所测量的数据。
b- ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
ISO 14644-1 为不同的企业提供一致的洁净室微粒浓度标准。ISO 5 的微粒浓度相当于 100 级，或大致相等于 EU A 级。
c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
粒子数测量值代表环境质量中的推荐水平。也可以依此并参考操作的方法和性质建立不同的微生物行动限标准。
d- The additional use of settling plates is optional.
另外使用沉降菌测试也是可选的。
e- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.
100 级(ISO5)环境中采的样品不应当有微生物污染。

Two clean areas are of particular importance to sterile drug product quality: the critical area and the supporting clean areas associated with it.

对无菌药品质量相当重要的两个区域是：关键区域和与之相连的支持清洁区域。

A. Critical Area – Class 100 (ISO 5)
关键区域－100 级（ISO 5)

A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility (§211.42(c)(10)). Activities conducted in such areas include manipulations (e.g., aseptic connections, sterile ingredient additions) of sterile materials prior to and during filling and closing operations.

关键区域是指当无菌药品及包装容器要暴露于生产环境的生产区域，这个生产环境必须设计得能够保持无菌条件（§211.42(c)(10)）。在此区间生产活动包括在灌装和密封之前无菌材料的操作（如：无菌连接，无菌药品成分添加）。

This area is critical because an exposed product is vulnerable to contamination and will not be subsequently sterilized in its immediate container. To maintain product sterility, it is essential that the environment in which aseptic operations (e.g., equipment setup, filling) are conducted be controlled and maintained at an appropriate quality. One aspect of environmental quality is the particle content of the air. Particles are significant because they can enter a product as an extraneous contaminant, and can also contaminate it biologically by acting as a vehicle for microorganisms (Ref. 2). Appropriately designed air handling systems minimize particle content of a critical area.

这个区域很关键，因为一个暴露的产品很容易被感染，在以后的包装中也不能再进行灭菌。为了保证产品无菌，在一定质量水平上控制和维护进行无菌操作（如设备安装，灌装）的环境是很重要的。环境质量的一个方面是空气中微粒的含量。空气中的微粒很重要因为它们可以成为外来污染成分进入产品，也可以成为微生物的载体来污染产品（参考2）。恰当设计的空气处理系统能减少关键区域的微粒成分。

Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations would be of appropriate particle quality when it has a per-cubic-meter particle count of no more than 3520 in a size range of 0.5 μm and larger when counted at representative locations normally not more than 1 foot away from the work site, within the airflow, and during filling/closing operations. This level of air cleanliness is also known as Class 100 (ISO 5).

在直接靠近暴露的消毒包装容器和灌封操作的空气，其 0.5μm 的微粒数应当不超过 3520 每立方米，而在工作点 1 英尺以外的测试点动态操作条件下的层流空气微粒数要大一些。这也就是洁净度为也是 100 级(ISO 5)的空气质量标准。

We recommend that measurements to confirm air cleanliness in critical areas be taken at sites where there is most potential risk to the exposed sterilized product, containers, and closures. The particle counting probe should be placed in an orientation demonstrated to obtain a meaningful sample. Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters. See Section X.E. for additional guidance on particle monitoring.

我们建议判断空气洁净标准的测量可在无菌产品，容器和胶塞最容易暴露的场所进行。微粒计数仪探头应在一个最意义的地方取样。每个生产班次都应进行日常监控 。我们建议用一个远程计数系统来进行静态的检测。这套系统能够收集更为广泛的数据，而且对环境的影响比手提式微粒计数器更小。关于微粒监测，请参照第十章第 E 部分。

Some operations can generate high levels of product (e.g., powder) particles that, by their nature, do not pose a risk of product contamination. It may not, in these cases, be feasible to measure air quality within the one-foot distance and still differentiate background levels of particles from air contaminants. In these instances, air can be sampled in a manner that, to the extent possible, characterizes the true level of extrinsic particle contamination to which the product is exposed. Initial qualification of the area under dynamic conditions without the actual filling function provides some baseline information on the non-product particle generation of the operation.

有些操作能产生高水平的产品微粒（如：粉剂），但这些微粒没有产品感染的危险。在这些情况下，在一英尺距离内测量空气质量，并仍然将微粒的背景程度与空气污染因素区分开是不太可能的。在这些情况下，空气可以在尽可能的方式下取样，以判断产品暴露地方的外来微粒的真实水平。最初没有进行灌装时的动态条件下的验证能提供操作时非产品微粒的基础信息。

HEPA-filtered[4] air should be supplied in critical areas at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations. The velocity parameters established for each processing line should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within the critical area (Ref. 3).[5]

在关键区域的 HEPA 过滤的[4]空气，其流速应当足够将灌封区域产生的微粒清除，并且能在操作区间维持层流。关键区域的每条生产线所设立的速度参数都应当规范，能适应于动态下保持空气层流以及空气质量（参考文献 3）。[5]

Proper design and control prevents turbulence and stagnant air in the critical area. Once relevant parameters are established, it is crucial that airflow patterns be evaluated for turbulence or eddy currents that can act as a channel or reservoir for air contaminants (e.g., from an adjoining lower classified area). In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. The studies should be well documented with written conclusions, and include evaluation of the impact of aseptic manipulations (e.g., interventions) and equipment design. Videotape or other recording mechanisms have been found to be useful aides in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes. It is important to note that even successfully qualified systems can be compromised by poor operational, maintenance, or personnel practices.

恰当的设计和控制能预防关键区域的紊流及空气滞留。一旦建立相应的参数，测量紊流或涡流空气的流动模式很重要，它们可以成为空气污染的渠道或仓库（如从临近低洁净级别带入）。现场空气流动模式分析应当在关键区域进行，以显示动态环境下层流及气流流过产品或离开产品时的流向。研究应当用书面形式总结，包括对无菌操作的影响（如干扰）及设备设计的评估。在气流和促进设备结构改变的评估方面，录像带或其他录像机器是很有用的。需要注意的是即使很成功合格的体系也可以被不适当的操作、维护或个人工作方式所危害。

Air monitoring samples of critical areas should normally yield no microbiological contaminants. We recommend affording appropriate investigative attention to contamination occurrences in this environment.

关键区域的空气监测通常不会带来微生物污染。我们建议应当调查并注意在这种境下污染的出现。

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[4]High Efficiency Particulate Air filter

[4] 高效颗粒空气过滤器

[5] A velocity of 0.45 meters/second (90 feet per minute) has generally been established, with a range of plus or minus 20 percent around the setpoint. Higher velocities may be appropriate in operations generating high levels of particulates.

[5] 通常规定的是每秒钟 0.45 米的风速（每分钟 90 英尺），允许上下 20%波动。高风速对于产生高水平颗粒的操作较合适。

B. Supporting Clean Areas
辅助洁净区

Supporting clean areas can have various classifications and functions. Many support areas function as zones in which nonsterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred. These environments are soundly designed when they minimize the level of particle contaminants in the final product and control the microbiological content (bioburden) of articles and components that are subsequently sterilized.

辅助洁净区有不同的分类和功能。许多辅助区是用于准备、保存及运输非无菌成分、成品、中间产品、设备和容器/胶塞的地方。这些区域设计合理，能降低终产品的微粒污染，控制产品灭菌之前的微生物成分(生物负荷)。

The nature of the activities conducted in a supporting clean area determines its classification. FDA recommends that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO 7) standards (see Table 1) under dynamic conditions. Manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5). An area classified at a Class 100,000 (ISO 8) air cleanliness level is appropriate for less critical activities (e.g., equipment cleaning).

在辅助区域进行的活动的性质决定了它的洁净级别。FDA 建议靠近无菌生产线的区域，应该在动态的环境下至少符合 10,000 级(ISO7)的标准（见表 1）。 生产商也可以将这个区域归类于 1,000 级(ISO6) 或保持整个无菌灌装室在 100 级(ISO 5) 的标准上。100,000 级(ISO8) 标准的洁净区域的适用于非关键的操作（如： 设备清洁）。

C. Clean Area Separation
净化区的隔离

An essential part of contamination prevention is the adequate separation of areas of operation. To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas. It is vital for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. For example, a positive pressure differential of at least 10-15 Pascals (Pa)[6] should be maintained between adjacent rooms of differing classification (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination, and it is critical that the time a door can remain ajar be strictly controlled (Ref. 4).

控制污染很重要的一个方面就是在生产操作时要有足够的区间分隔。 为了保持空气质量，将空气流向从更清洁的区域流向临近的不太清洁的区域是很重要的。更高级别的洁净区域相对于不太高级别的临近区域有足够的正压差，这是很重要的。比如: 在两个洁净级

[6] Equal to 0.04-0.06 inches of water gauge.

[6] 相等于 0.04—0.06 英寸水标。

别的临近房间之间至少要保持 10-15Pa [6]的压差（门关闭时）。房门打开时，要有足够的向外气流来减少污染的侵入，而且房门打开的时间要严格控制（参考文献 4）。

In some cases, the aseptic processing room and adjacent cleanrooms have the same classification. Maintaining a pressure differential (with doors closed) between the aseptic processing room and these adjacent rooms can provide beneficial separation. In any facility designed with an unclassified room adjacent to the aseptic processing room, a substantial overpressure (e.g., at least 12.5 Pa) from the aseptic processing room should be maintained at all times to prevent contamination. If this pressure differential drops below the minimum limit, it is important that the environmental quality of the aseptic processing room be restored and confirmed.

在一些情况下，无菌操作室和附近的洁净室在同样的洁净级别下。在无菌操作室和这些临近洁净室之间保持压差（房门关闭的情况下）可以提供有益的隔离。如果有无洁净级别的房间与无菌操作房相临的设计，则应该随时保持从无菌操作间向外的足够的压差（如：至少 12.5Pa)来防止感染。如果这个压差降低到最小值下，无菌操作间的环境质量必须得要恢复并且确认，这点很重要。

The Agency recommends that pressure differentials between cleanrooms be monitored continuously throughout each shift and frequently recorded. All alarms should be documented and deviations from established limits should be investigated.

FDA 建议要在洁净室间每一个班次连续使用压差监控并经常记录。所有警戒限都要记录在文件上，超出警戒限的偏差都要进行调查。

Air change rate is another important cleanroom design parameter. For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas.

换气次数是另一个重要的洁净室设计参数。对于 100,000 级(ISO8)的辅助房间，能够达到每小时 20 次的换气次数是可以接受的。对于 10,000 级和 100 级区域，通常需要更高一些的换气次数。

A suitable facility monitoring system will rapidly detect atypical changes that can compromise the facility's environment. An effective system facilitates restoration of operating conditions to established, qualified levels before reaching action levels. For example, pressure differential specifications should enable prompt detection (i.e., alarms) of an emerging low pressure problem to preclude ingress of unclassified air into a classified room.

一个恰当的设备监控系统能很快监测出有可能影响环境的非典型变化。一个有效的系统能在达到行动限之前恢复设定的合格的操作状态。比如：设定压差控制限可以加快意外低压问题出现时的反应（如报警），这样可以预防不洁净的空气进入洁净室。

D. Air Filtration
空气过滤

1. Membrane
膜过滤

A compressed gas should be of appropriate purity (e.g., free from oil) and its microbiological and particle quality after filtration should be equal to or better than that of the air in the environment into which the gas is introduced. Compressed gases such as air, nitrogen, and carbon dioxide are often used in cleanrooms and are frequently employed in purging or overlaying.

压缩气体应该有恰当的纯度（如无油），过滤后的微生物及微粒数应当等同或超过使用气体的环境的洁净度。压缩气体象空气，氮气，二氧化碳经常用在洁净室中，用于清洗及保护覆盖。

Membrane filters can be used to filter a compressed gas to meet an appropriate high-quality standard. These filters are often used to produce a sterile compressed gas to conduct operations involving sterile materials, such as components and equipment. For example, we recommend that sterile membrane filters be used for autoclave air lines, lyophilizer vacuum breaks, and tanks containing sterilized materials. Sterilized holding tanks and any contained liquids should be held under positive pressure or appropriately sealed to prevent microbial contamination. Safeguards should be in place to prevent a pressure change that can result in contamination due to back flow of nonsterile air or liquid.

膜过滤可以用来过滤压缩空气，使之达到恰当的高质量水平。这些过滤器经常用来生产无菌压缩空气，进行与无菌材料，如成分和设备相关操作。如：我们建议将无菌膜过滤器用于蒸汽灭菌器的进气口，冷冻干燥机真空保护器及装无菌物料的储罐。经灭菌的储存罐以及所储存的液体应正压保护或密封储存以防止微生物的感染。安全措施应当到位，以防止压差改变引起非无菌气体或液体的回流产生的感染。

Gas filters (including vent filters) should be dry. Condensate on a gas filter can cause blockage during use or allow for the growth of microorganisms. Use of hydrophobic filters, as well as application of heat to these filters where appropriate, prevents problematic moisture residues. We recommend that filters that serve as sterile boundaries or supply sterile gases that can affect product be integrity tested upon installation and periodically thereafter (e.g., end of use). Integrity tests are also recommended after activities that may damage the filter. Integrity test failures should be investigated, and filters should be replaced at appropriate, defined intervals.

气体过滤器（包括排气过滤）应当是干燥的。气体过滤器上的冷凝液会导致微生物繁殖而引起堵塞。使用疏水性过滤器以及在这些过滤器上加热以防止类似潮湿所引起的问题。我们建议在安装及以后，对用于无菌阻隔或过滤的，会影响产品质量的无菌气体的过滤器，进行周期性（如，使用后）完整性测试。有可能破坏过滤器的过滤完成后也推荐进行完整性测试。完整性测试失败的应当进行调查，同时应定期地更换过滤器。

2. High-Efficiency Particulate Air (HEPA)[7]
高效颗粒空气过滤器(HEPA)[7]

HEPA filter integrity should be maintained to ensure aseptic conditions. Leak testing should be performed at installation to detect integrity breaches around the sealing gaskets, through the frames, or through various points on the filter media. Thereafter, leak tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room. Additional testing may be appropriate when air quality is found to be unacceptable, facility renovations might be the cause of disturbances to ceiling or wall structures, or as part of an investigation into a media fill or drug product sterility failure. Among the filters that should be leak tested are those installed in dry heat depyrogenation tunnels and ovens commonly used to depyrogenate glass vials. Where justified, alternate methods can be used to test HEPA filters in the hot zones of these tunnels and ovens.

应保持高效过滤器的完整性以确保无菌环境。高效过滤器的泄漏测试应当在安装时就进行，以检测在密封圈周围，框架周围或过滤介质上的泄漏。所以，无菌操作设施上的高效过滤器的泄漏测试应当定期进行。例如：无菌操作间的此类检测应当一年进行两次。当空气质量不理想时，可以进行额外实验，设备更新可能会导致天花板，或墙面结构的破坏，或导致培养基灌装试验或药品的无菌性的破坏。包括安装在隧道烘箱和用于玻璃瓶去热源的干热灭菌器中的过滤器也应当进行泄漏测试。在有充分理由的情况下，可以用其它方法检查在这些隧道和烘箱等加热区域的高效过滤器。

Any aerosol used for challenging a HEPA filter should meet specifications for critical physicochemical attributes such as viscosity. Dioctylphthalate (DOP) and poly-alpha-olefin (PAO) are examples of appropriate leak testing aerosols. Some aerosols are problematic because they pose the risk of microbial contamination of the environment being tested. Accordingly, the evaluation of any alternative aerosol involves ensuring it does not promote microbial growth.

任何用于高效过滤器的检漏测试的气溶胶应当符合关键物理化学特性的规格，如粘度。DOP 和 PAO 就是两种经常用于检漏测试的气溶胶。有些气溶胶会带来问题，因为它们可能会携带微生物而污染被测试的环境。因此，衡量气溶胶的替代物包括保证它是不会促进微生物的增长。

There is a major difference between *filter leak testing* and *efficiency testing*. An efficiency test is a general test used to determine the rating of the filter.[8] An intact HEPA filter should be capable of retaining at least 99.97 percent of particulates greater than 0.3 μm in diameter.

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[7] The same broad principles can be applied to ULPA filters.
[7] 同样的主要原则可应用于 ULPA 滤器。

[8] The efficiency test uses a monodispersed aerosol of 0.3 micron sized particles and assesses filter media. Downstream readings represent an average over the entire filter surface. Efficiency tests are not intended to test for filter leaks.

[8] 效率测试用一个 0.3 微米大小颗粒的单一分散气溶胶，并评价过滤介质。下游读数代表整个过滤表面的平均数。效率测试不适用于滤器检漏。

过滤器泄漏测试和有效性测试之间有很大的区别。有效性测试是用来判断过滤器的过滤率[8]。一个完整的高效过滤器应当能保留直径大于 0.3μm 的微粒至少在 99.97%以上。

The purpose of performing regularly scheduled leak tests, on the other hand, is to detect leaks from the filter media, filter frame, or seal. The challenge involves use of a polydispersed aerosol usually composed of particles with a light-scattering mean droplet diameter in the submicron size range,[9] including a sufficient number of particles at approximately 0.3 μm. Performing a leak test without introducing a sufficient upstream challenge of particles of known size upstream of the filter is ineffective for detecting leaks. It is important to introduce an aerosol upstream of the filter in a concentration that is appropriate for the accuracy of the aerosol photometer. The leak test should be done in place, and the filter face scanned on the downstream side with an appropriate photometer probe, at a sampling rate of at least one cubic foot per minute. The downstream leakage measured by the probe should then be calculated as a percent of the upstream challenge. An appropriate scan should be conducted on the entire filter face and frame, at a position about one to two inches from the face of the filter. This comprehensive scanning of HEPA filters should be fully documented.

定期进行泄漏测试的目的，从另一方面而言，是为了检查过滤介质，过滤器框架和密封的泄漏。用于测试的多分散气溶胶中包含微米级直径的光散射微粒[9]，其中很多微粒大约 0.3μm 左右。如果不在过滤器上游使用充足的已知直径的微粒进行泄漏测试是没有意义的。在过滤器上游使用准确浓度的气溶胶是很重要的。泄漏测试可以在原位进行，在过滤面下游用光电探测头以每分钟 1 个立方英尺的取样速度进行扫描测试。这样下游的泄漏就可以用探头测量出来，然后可计算出占上游的百分比。在离过滤器表面 1 到 2 英寸的地方扫描经过整个过滤器和框架的表面。这个复杂的高效过滤器的扫描过程需文件记录。

A single probe reading equivalent to 0.01 percent of the upstream challenge would be considered as indicative of a significant leak and calls for replacement of the HEPA filter or, when appropriate, repair in a limited area. A subsequent confirmatory retest should be performed in the area of any repair.

上游浓度 0.01%的泄漏率就可以被认作是严重泄漏，应当更换高效过滤器或在有限的地方进行维修，如可能的话。任何维修的地方需进行随后的确认重测试。

HEPA filter leak testing alone is insufficient to monitor filter performance. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity can cause turbulence that increases the possibility of contamination. Velocities of unidirectional air should be measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area. Velocity monitoring at suitable intervals can provide useful data on the critical area in which aseptic processing is performed. The measurements should correlate to the velocity

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[9] Although the mean is normally less than one micron, it is greater than 0.3μm.

[9] 虽然平均数通常小于 1 微米，但它大于 0.3mm。

range established at the time of in situ air pattern analysis studies. HEPA filters should be replaced when nonuniformity of air velocity across an area of the filter is detected or airflow patterns may be adversely affected.

仅高效过滤器泄漏测试的一项测试不足以监控过滤器的所有性能。定期进行过滤器的过滤面风速（以及考虑临近过滤器的影响）一致性测试也是很重要的。风速的变化可以导致紊流增加污染的可能性。单向空气流的速度测试可以在离过滤器表面 6 英寸的地方进行，或在关键区域接近工作面的距离进行。定期的速度检测可以提供无菌操作的关键区域的有用的数据资料。测量应当结合现场气流模式分析研究时候所建立的速度范围进行。当在过滤器的覆盖的地方的发现气流速度不一致，或气流模式受负面影响时，应当更换高效过滤器。

Although contractors often provide these services, drug manufacturers are responsible for ensuring that equipment specifications, test methods, and acceptance criteria are defined, and that these essential certification activities are conducted satisfactorily.

虽然供应商通常会提供这类服务，但药品生产商要负责保证如设备特性要求、测试方法和接受限等，已确定这些测试服务进行得令人满意。

E. Design
设计

Note: The design concepts discussed within this section are not intended to be exhaustive. Other appropriate technologies that achieve increased sterility assurance are also encouraged.

注意：在这章所讨论的设计概念只是简略的介绍。我们也鼓励能够使无菌保证效果增加的技术。

Aseptic processes are designed to minimize exposure of sterile articles to the potential contamination hazards of the manufacturing operation. Limiting the duration of exposure of sterile product elements, providing the highest possible environmental control, optimizing process flow, and designing equipment to prevent entrainment of lower quality air into the Class 100 (ISO 5) clean area are essential to achieving high assurance of sterility (Ref. 4).

设计无菌操作过程是为了减少无菌药品在生产操作过程中暴露受污染的危险。减少无菌成分的暴露时间，提供最大可能的环境控制，优化生产流程，设计设备以防止低质量的空气侵入 100 级 (ISO 5)的洁净区， 这些过程对获得高无菌保证非常关键（参考文献 4）。

Both personnel and material flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures, or the surrounding environment. The layout of equipment should provide for ergonomics that optimize comfort and movement of operators. The number of personnel in an aseptic processing room should be minimized. The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from an aseptic processing room and, most significant, its critical area. Regarding the latter, the number of transfers into the critical area of

a traditional cleanroom, or an isolator, should be minimized. To prevent changes in air currents that introduce lower quality air, movement adjacent to the critical area should be appropriately restricted.

应当优化人员和物料流程以减少不必要的活动，防止增加对暴露产品，容器或周围环境的潜在污染的可能。设备的摆设应当从人体工程学的角度出发适应操作人员的舒适和行动。在无菌操作间的人员数量应当尽量少。人员的流动应当设计得可以限制人员进出无菌操作室和关键生产区域的次数。说到后者，进入传统洁净室或隔离箱等关键区域的次数要减少。为了防止气流的变化带入低质空气，临近关键区域的活动都要适当控制。

Any intervention or stoppage during an aseptic process can increase the risk of contamination. The design of equipment used in aseptic processing should limit the number and complexity of aseptic interventions by personnel. For example, personnel intervention can be reduced by integrating an on-line weight check device, thus eliminating a repeated manual activity within the critical area. Rather than performing an aseptic connection, sterilizing the preassembled connection using sterilize-in-place (SIP) technology also can eliminate a significant aseptic manipulation. Automation of other process steps, including the use of technologies such as robotics, can further reduce risk to the product.

任何无菌操作期间的干扰或停止都有可能增加污染的危险。无菌操作所用的设备的应设计得能限制和减少由人员引起的无菌干扰。比如：如果引进一个在线重量检测装置，就可以减少人员在关键区域的重复手工活动。将预先连接的装置用在线灭菌（SIP）技术消毒，而不是进行灭菌后的无菌连接操作，这样也可以有效减少无菌操作。自动化操作其它的步骤，包括用象机器人技术等，可以进一步减少产品的污染危险。

Products should be transferred under appropriate cleanroom conditions. For example, lyophilization processes include transfer of aseptically filled product in partially sealed containers. To prevent contamination, a partially closed sterile product should be transferred only in critical areas.[10] Facility design should ensure that the area between a filling line and the lyophilizer provide for Class 100 (ISO 5) protection. Transport and loading procedures should afford the same protection.

产品也应当在适当的洁净室条件下转移。比如，冻干程序中转移部分密封的无菌灌装产品后的容器。为了防止污染，部分密封的无菌产品只能在关键区域内转移。[10]设备设计就应当确保能在灌装线和冷冻干燥机之间的区域提供 100 级 (ISO5)保护。运输和装载程序应当能提供同样的保护。

The sterile drug product and its container-closures should be protected by equipment of suitable design. Carefully designed curtains and rigid plastic shields are among the barriers that can be used in appropriate locations to achieve segregation of the aseptic processing line. Use of an isolator system further enhances product protection (see Appendix 1).

[10] Appropriately designed transfer equipment provides these conditions and can be qualified for this purpose.

[10] 合理设计的转移设备提供这些条件，并能够就次进行确认。

无菌产品和它的容器应当有适当设计的设备保护。在恰当地方精细设计的窗帘和硬质塑料围布都可以用来作为保护屏障，以达到隔离无菌生产线的目的。隔离箱的使用进一步增强了产品的保护(见附录 1)。

Due to the interdependence of the various rooms that make up an aseptic processing facility, it is essential to carefully define and control the dynamic interactions permitted between cleanrooms. Use of a double-door or integrated sterilizer helps ensure direct product flow, often from a lower to a higher classified area. Airlocks and interlocking doors will facilitate better control of air balance throughout the aseptic processing facility. Airlocks should be installed between the aseptic manufacturing area entrance and the adjoining unclassified area. Other interfaces such as personnel transitions or material staging areas are appropriate locations for air locks. It is critical to adequately control material (e.g., in-process supplies, equipment, utensils) as it transfers from lesser to higher classified clean areas to prevent the influx of contaminants. For example, written procedures should address how materials are to be introduced into the aseptic processing room to ensure that room conditions remain uncompromised. In this regard, materials should be disinfected according to appropriate procedures or, when used in critical areas, rendered sterile by a suitable method.

由于组成无菌生产线的各设备的所在不同房间的相互依赖，在洁净室之间控制动态的相互作用是非常重要。用双扉或在线的灭菌器能帮助产品直接的流动，通常从低洁净级别流向高级别。在无菌生产设备中使用风淋或连锁门可以更好的控制空气平衡。风淋应当装在无菌生产间入口和临近的无级别的区域。其它象人员进出或堆放物料的地方是装气锁的适合的地方。适当控制物料（如： 在线供应，设备，容器）从较低级别进入高级别洁净室是很关键的，因为这样可以控制污染的入侵。比如：可以用书面程序来说明怎样将物料放入无菌操作室，以确保房间环境保持不受污染。因此，使用于关键区域的物料应当根据适当的程序进行消毒或使用其他的恰当方式来提供无菌。

If stoppered vials exit an aseptic processing zone or room prior to capping, appropriate assurances should be in place to safeguard the product, such as local protection until completion of the crimping step. Use of devices for on-line detection of improperly seated stoppers can provide additional assurance.

如果加塞的小瓶在压盖之前就退出无菌生产区或房间的，恰当的保证措施应当到位，就象在加盖卷边之前有现场的保护措施。用在线检查装置来检查没有完全密封的塞子可以提供更多的安全保证。

Cleanrooms are normally designed as functional units with specific purposes. The materials of construction of cleanrooms ensure ease of cleaning and sanitizing. Examples of adequate design features include seamless and rounded floor to wall junctions as well as readily accessible corners. Floors, walls, and ceilings should be constructed of smooth, hard surfaces that can be easily cleaned. Ceilings and associated HEPA filter banks should be designed to protect sterile materials from contamination. Cleanrooms also should not contain unnecessary equipment, fixtures, or materials.

洁净室通常作为功能单位来有目的地设计。洁净室的建筑材料要确保便于清洁和消毒。适当的设计如无缝的地板以及圆弧形的地面与墙面的转角，以及容易打扫得到的角落。地板，墙面及天花板应该用光滑，坚硬的材料建成，易于打扫。天花板和与之连接的高效过滤器边缘应当设计得可以避免无菌物料受污染。洁净室内也不应该放置不必要的设备，装置，或物料。

Processing equipment and systems should be equipped with sanitary fittings and valves. With rare exceptions, drains are considered inappropriate for classified areas of the aseptic processing facility other than Class 100,000 (ISO 8) areas. It is essential that any drain installed in an aseptic processing facility be of suitable design.

加工设备和系统应当使用卫生装置和卫生阀门。大多数情况下，在除十万级（ ISO8）的洁净室之外的无菌操作洁净室中安放排水沟被认为是不恰当的。而且在无菌操作洁净室中装置排水沟应当有恰当的设计。

Equipment should be appropriately designed (§211.63) to facilitate ease of sterilization. It is also important to ensure ease of installation to facilitate aseptic setup. The effect of equipment design on the cleanroom environment should be addressed. Horizontal surfaces or ledges that accumulate particles should be avoided. Equipment should not obstruct airflow and, in critical areas, its design should not disturb unidirectional airflow.

设备应恰当设计以方便消毒，能保证无菌安装的方便也很重要。设备设计对洁净室环境的影响也应当受重视。水平表面和突出物上会堆积尘埃粒子，应当避免。设备不应该阻挡气流，在关键区域，它的设计不应该影响层流。

Deviation or change control systems should address atypical conditions posed by shutdown of air handling systems or other utilities, and the impact of construction activities on facility control. Written procedures should address returning a facility to operating conditions following a shutdown.

偏差或变更控制系统中应当提及非典型状况，如由于空气处理系统或其它设备断电所引起的，以及建筑活动对设备控制的影响。应当有书面程序说明怎样在关机之后将设备恢复正常运转。

V. PERSONNEL TRAINING, QUALIFICATION, & MONITORING

21 CFR 211.22(a) states that "There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company."

CFR211.22(a)规定，"应当有一个质量控制部门，它有职责和权利接受或拒绝所有制药成分、药品容器、胶塞、中间品、包装材料、标签和成品，也有权利检查生产记录以确保生产过程中没有发生错误,或即使有错误,也能得到及时全面的调查。质量控制部门也应当有责任接受或拒绝其他合同签约公司生产的产品，、中间品、包装品或暂存品。"

21 CFR 211.22(c) states that "The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product."

CFR211.22(c)规定，"质量控制部门应当有责任接受或拒绝所有影响药品成分、浓度，质量及纯度的操作程序和接受标准。"

21 CFR 211.25(a) states that "Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them."

CFR211.25(a)规定，"每一个涉及药品生产、加工、包装及储存的人员都应当受过教育、培训、有经验或相关的资质，使之能够完成指定的任务。培训应当着重员工要操作的内容和现行的 GMP(包括此章中提到的现行生产操作规范及这些法规所要求的书面程序)，这些与员工切实相关。CGMP 的培训应当由合格的人员来持续频繁地进行，以确保员工熟悉适用于他们的 CGMP 的要求。"

21 CFR 211.25(b) states that "Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess."

21CFR211.25(b)规定，"每个负责于生产，加工，包装及储存药品的监督人员都应当受过相关的教育、培训、有经验或相关的资质，来完成指定的任务，以确保药品有它应有的安全、成分、浓度、质量以及纯度。"

21 CFR 211.25(c) states that "There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product."

CFR211.25(c)规定，"应当有足够数量的合格的人员来操作和监督每个药品的生产、加工、包装及储存。"

21 CFR 211.28(a) states that "Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination."

CFR211.28(a)规定，"与药品的生产，加工，包装及储存有关的人员都应当穿着与他们的工作相适应的干

净衣物。必须穿着象头套，脸套，手套，及手臂套等防护着装，以防药品感污染。”

21 CFR 211.28(b) states that “Personnel shall practice good sanitation and health habits.”

CFR 211.28(b) 规定，“员工应当有良好的卫生和健康习惯。”

21 CFR 211.28(c) states that “Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.”

21 CFR 211.28(c) 规定，“只有监督人员授权的员工才能进入规定为限制进入的建筑和设施。”

21 CFR 211.28(d) states that “Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.”

21CFR211.28(d)规定，“任何人员发现（不论是经诊断或主管察觉）有明显生病迹象或开放性的伤口，有可能会影响药品的安全或质量的，都不能与药品成分、包装容器、胶塞、中间品和成品有直接接触，直到病情好转，或由合格医疗人员确证不再危害药品的安全与质量后方可回到工作岗位。”

21 CFR 211.42(c) states, in part, that “Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination or mixups during the course of the following procedures: * * * (10) Aseptic processing, which includes as appropriate: * * * (iv) A system for monitoring environmental conditions * * *.”

21CFR211.42(c)部分规定，“操作应当在足够空间的指定区域进行。公司的生产操作必须有隔离或指定的区域或类似其它的控制区域，来防止在以下生产过程中的污染或混杂：…（10）无菌操作，比如象….(iv) 环境控制系统…。”

21 CFR 211.113(b) states that “Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.”

21 CFR 211.113(b) 规定，“应当建立及依从防止无菌药品受微生物污染的书面程序。此程序应当包括消毒过程的验证。”

A. Personnel
人员

A well-designed, maintained, and operated aseptic process minimizes personnel intervention. As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases. To ensure maintenance of product sterility, it is critical for operators involved in aseptic activities to use aseptic technique at all times.

一个良好设计、维持及操作的无菌过程能减少人员的影响。因为人员操作会增加在无菌生产过程中的操作步骤，也会增加污染无菌药品的机会。为了确保维持产品无菌,与无菌生产过程相关的操作人员必须随时使用无菌技术。

Appropriate training should be conducted before an individual is permitted to enter the aseptic manufacturing area. Fundamental training topics should include aseptic technique, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards posed by a nonsterile drug product, and the specific written procedures covering aseptic manufacturing area operations. After initial training, personnel should participate regularly in an ongoing training program. Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations. Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures and aseptic technique during manufacturing operations.

在允许人员进入无菌生产区域之前应当进行适当的培训。基本的培训课题应当包括无菌技术、洁净室行为规范、微生物学、卫生学，着装程序、由非无菌药品带给患者的安全危害，以及无菌生产区域操作规范的书面程序。在首期培训后，人员应当定期参加持续的培训课程。主管应当定期评估操作者在实际操作中符合书面程序的程度。同样的，质量控制部门应当定期检查，以确保书面的程序与实际生产操作中的无菌技术相符合。

Some of the techniques aimed at maintaining sterility of sterile items and surfaces include:

一些维护无菌产品和表面的无菌性的技术包括：

- Contact sterile materials only with sterile instruments

  只能用无菌设备接触无菌物料。

  Sterile instruments should always be used in the handling of sterilized materials. Between uses, sterile instruments should be held under Class 100 (ISO 5) conditions and maintained in a manner that prevents contamination (e.g., placed in sterilized containers). Instruments should be replaced as necessary throughout an operation.

  在处理无菌物料时应始终使用无菌器具。在使用过程中，无菌器具要保存在 100 级（ISO5）的环境中并防止污染的状态（如放在无菌容器中）。在操作过程中如有需要要及时更换器具。

  After initial gowning, sterile gloves should be regularly sanitized or changed, as appropriate, to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces with any part of their gown or gloves.

  在基本着装之后，无菌手套应当定期消毒或更换，以减少污染的危险。操作人员衣服或手套的任何部分不能直接接触无菌药品，容器，胶塞或关键的表面。

- Move slowly and deliberately

  有目的的慢速地行动

Rapid movements can create unacceptable turbulence in a critical area. Such movements disrupt the unidirectional airflow, presenting a challenge beyond intended cleanroom design and control parameters. The principle of slow, careful movement should be followed throughout the cleanroom.

快速运动可能会在关键区域导致不可接受的紊流。这种快速运动会干扰层流，造成与洁净室的设计和控制不符合的情况。在整个洁净室内必须依从缓慢的，小心地行动的规则。

- Keep the entire body out of the path of unidirectional airflow

避免身体任何部分挡住层流的路线

Unidirectional airflow design is used to protect sterile equipment surfaces, container-closures, and product. Disruption of the path of unidirectional flow air in the critical area can pose a risk to product sterility.

层流设计是为了保护无菌设备的表面、容器、胶塞以及产品。在关键区域挡住层流的路线会给无菌药品带来污染的危险。

- Approach a necessary manipulation in a manner that does not compromise sterility of the product

采用不影响药品无菌性的操作方式

To maintain sterility of nearby sterile materials, a proper aseptic manipulation should be approached from the side and not above the product (in vertical unidirectional flow operations). Also, operators should refrain from speaking when in direct proximity to the critical area.

为了保持无菌物料附近的无菌状态，一个正确的无菌操作方式应当是从物料旁边，而不是从物料上面来接近物料（在垂直层流下的操作）。而且，操作人员应当避免在关键区域附近交谈。

- Maintain Proper Gown Control

维持正确的着装控制

Prior to and throughout aseptic operations, an operator should not engage in any activity that poses an unreasonable contamination risk to the gown.

在无菌操作之前和在整个操作期间，操作人员不应当涉及任何会给衣物带来不合理污染的活动。

Only personnel who are qualified and appropriately gowned should be permitted access to the aseptic manufacturing area. The gown should provide a barrier between the body and exposed

sterilized materials and prevent contamination from particles generated by, and microorganisms shed from, the body. The Agency recommends gowns that are sterilized and nonshedding, and cover the skin and hair (face-masks, hoods, beard/moustache covers, protective goggles, and elastic gloves are examples of common elements of gowns). Written procedures should detail the methods used to don each gown component in an aseptic manner. An adequate barrier should be created by the overlapping of gown components (e.g., gloves overlapping sleeves). If an element of a gown is found to be torn or defective, it should be changed immediately. Gloves should be sanitized frequently.

只有合格、正确着装的人员才可以允许进入无菌生产区域。衣服应当在身体和暴露的无菌物料之间提供屏障，防止从身体上脱落或产生的微粒和微生物污染无菌物料。FDA 建议衣服应当经过消毒而且无脱落，能盖住皮肤和头发（面罩，头套， 胡须套，防护眼镜和有弹性的手套是着装的一般组成部分）。应当用书面程序详细描述着装的无菌操作规程的每个细节。衣服与衣服之间要有重叠，形成充分屏障（如手套要叠住衣服的袖口）。如果衣服的某一部分撕裂或有缺陷，应当立即更换衣服。手套应当经常消毒。

There should be an established program to regularly assess or audit conformance of personnel to relevant aseptic manufacturing requirements. An aseptic gowning qualification program should assess the ability of a cleanroom operator to maintain the quality of the gown after performance of gowning procedures. We recommend that this assessment include microbiological surface sampling of several locations on a gown (e.g., glove fingers, facemask, forearm, chest). Sampling sites should be justified. Following an initial assessment of gowning, periodic requalification will provide for the monitoring of various gowning locations over a suitable period to ensure consistent acceptability of aseptic gowning techniques. Annual requalification is normally sufficient for those automated operations where personnel involvement is minimized and monitoring data indicate environmental control. For any aseptic processing operation, if adverse conditions occur, additional or more frequent requalification could be indicated.

应当有确定的程序，定时评估或审核操作人员与相关无菌操作要求的符合性。应有无菌着装确认程序，评价洁净室的操作人员在着装结束后保持服装无菌状态的能力。我们建议所述确认程序包括在衣服的几个地方（比如：手套手指、脸罩、前臂、胸部等）进行微生物表面取样。取样部位应当是恰当的。对着装进行初次评定后，应当提供周期性的再确认，以便在合适的周期内监控衣服的不同部位，确保持续有效的无菌着装技术。在那些人员参与的活动不多、环境监测资料提示控制良好的自动化操作，每年再确认一次就够了。对于任何无菌加工操作，如果出现不利情况，可以采用多次再确认。

To protect exposed sterilized product, personnel should to maintain gown quality and strictly adhere to appropriate aseptic techniques. Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas.

为了保护暴露的无菌物料，人员应当维持衣服的无菌状态，严格执行适当的无菌操作流程。应当有书面程序，规定何种情况下人员需要重新培训、再确认或重新安排到其他区域。

B. Laboratory Personnel
实验室人员

The basic principles of training, aseptic technique, and personnel qualification in aseptic manufacturing also are applicable to those performing aseptic sampling and microbiological laboratory analyses. Processes and systems cannot be considered to be in control and reproducible if the validity of data produced by the laboratory is in question.

无菌生产过程中的培训、无菌技术和人员确认的基本原则，也适用于无菌取样和微生物实验室的分析。如果对实验室产生的数据的有效性有疑问，流程和系统就不能被认为是在控制之内的和可重复的。

C. Monitoring Program
监测程序

Personnel can significantly affect the quality of the environment in which the sterile product is processed. A vigilant and responsive personnel monitoring program should be established. Monitoring should be accomplished by obtaining surface samples of each operator's gloves on a daily basis, or in association with each lot. This sampling should be accompanied by an appropriate sampling frequency for other strategically selected locations of the gown (Ref. 5). The quality control unit should establish a more comprehensive monitoring program for operators involved in operations which are especially labor intensive (i.e., those requiring repeated or complex aseptic manipulations).

人员可能显著影响无菌生产区域的环境质量。应当建立一个灵敏的能快速反应的人员监控程序。检测应当包括每天或每批生产后检查每个操作者的手套表面。该取样测试也应当包括定期选取衣服的某些重要部位进行检测（参考 5）。质量控制部门应当针对劳动强度大的操作人员（即那些需要进行重复或复杂无菌操作的），建立一个更完整的检测程序。

Asepsis is fundamental to an aseptic processing operation. An ongoing goal for manufacturing personnel in the aseptic processing room is to maintain contamination-free gloves and gowns throughout operations. Sanitizing gloves just prior to sampling is inappropriate because it can prevent recovery of microorganisms that were present during an aseptic manipulation. When operators exceed established levels or show an adverse trend, an investigation should be conducted promptly. Follow-up actions can include increased sampling, increased observation, retraining, gowning requalification, and in certain instances, reassignment of the individual to operations outside of the aseptic manufacturing area. Microbiological trending systems, and assessment of the impact of atypical trends, are discussed in more detail under Section X. Laboratory Controls.

无菌技术是无菌生产运作的基础。在无菌生产间的操作人员的目标之一就是要在整个操作中保持手套和衣服的无污染。在取样前消毒手套是不合适的，因为它会影响在无菌操作过程中污染微生物的回收率。当操作者的检查结果超过设定的标准或出现不良趋势时，应当马上开始调查工作。随后的措施包括增加取样量、密切关注、重新培训、着装的再确认，

在一些情况下,重新布置无菌生产区间以外的人员。微生物趋势分析，以及非典型趋势影响的评估，会在第 10 章：实验室控制中有详细的描述。

VI. COMPONENTS AND CONTAINER/CLOSURES
药品成分和容器/密封

21 CFR 210.3(b)(3) states that "*Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product."

21CFR210.3(b)规定，"药品成分是指任何药品生产中使用的成分,包括那些可能不出现在药品成品中的成分。"

21 CFR 211.80(a) states that "There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed."

CFR211.80(a)规定，"应当有书面的程序详细地描述接收、鉴别、储存、处理、取样、测试以及批准或拒绝药品成分和容器。 这些书面程序应当确实被采用。"

21 CFR 211.80(b) states that "Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination."

21CFR211.80(b)规定，"药品成分和药品包装容器应当始终有合适的方法来防止感染。"

21 CFR 211.84(d) states, in part, that "Samples shall be examined and tested as follows: * * * (6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use."

CFR211.84(d)部分规定，"样品应当如下检测….（6）每一批有可能受微生物污染而影响既定用途的药品成分，包装容器和胶塞，在打算使用前，应当进行微生物检测。"

21 CFR 211.94(c) states that "Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use."

CFR211.94(c)规定，"药品包装容器和胶塞应当保持洁净，而且，依据药品的特性的不同，应当消毒和除热源，以确保药品适合它的使用特性。"

21 CFR 211.94(d) states that "Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures."

21CFR211.94(d)规定，"药品包装容器和胶塞的标准，规格，测试方式，以及清洁，消毒和除热源方法应当书面记录并跟踪。"

21 CFR 211.113(b) states that "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."

21CFR211.113（b）规定"应当建立预防无菌药品的微生物污染的书面程序。这类程序应当包括无菌过程的验证。"

A. Components
药品成分

A drug product produced by aseptic processing can become contaminated through the use of one or more components that are contaminated with microorganisms or endotoxins. Examples of components include active ingredients, Water for Injection (WFI), and other excipients. It is important to characterize the microbial content (e.g., bioburden, endotoxin) of each component that could be contaminated and establish appropriate acceptance limits.

无菌生产的药品可能会由于其中一个或多个成分被微生物或内毒素的污染而受到污染。这些成分的包括活性原料、注射用水和其它赋形剂。找出每种成分可能被感染的物质（如：生物负荷，内毒素），建立恰当的合格标准，这是很重要的。

Endotoxin load data are significant because parenteral products are intended to be nonpyrogenic. There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins. Any components failing to meet defined endotoxin limits should be rejected.

内毒素数据很重要，因为注射用药产品应该是无热源的。应当有书面程序和恰当标准，以此为据，接受或拒绝每批可能包含内毒素的成分。任何成分的内毒素含量没有符合既定限度的，都应当被拒绝。

In aseptic processing, each component is individually sterilized or several components are combined, with the resulting mixture sterilized.[11] Knowledge of bioburden is important in assessing whether a sterilization process is adequate. Several methods can be suitable for sterilizing components (see relevant discussion in Section IX). A widely used method is filtration of a solution formed by dissolving the component(s) in a solvent such as Water For Injection, USP. The solution is passed through a sterilizing membrane or cartridge filter. Filter sterilization is used where the component is soluble and is likely to be adversely affected by heat. A variation of this method includes subjecting the filtered solution to aseptic crystallization and precipitation (or lyophilization) of the component as a sterile powder. However, this method involves more handling and manipulation and therefore has a higher potential for contamination during processing.

在无菌加工过程中，每种成分要分别灭菌或几种成分混合后最终灭菌。[11]生物负荷的知识对评估一个灭菌过程是否合适很重要。对药品成分的灭菌可以有许多方法（参考第 9 章的相关讨论）。最常用的方法是将成分溶解到 USP 注射用水等溶剂中，然后对溶液进行过滤。溶液通过一个灭菌过滤膜或过滤器来进行过滤。当成分可溶而且不耐热时，采用过滤除菌。另一个类似的方法是将需灭菌的成分无菌过滤结晶（或冻干）后，成为无菌粉末。然而，这个方法需要更多的操作处理，因此在加工过程中受污染的可能性更大。

Dry heat sterilization is a suitable method for components that are heat stable and insoluble. However, conducting carefully designed heat penetration and distribution studies is of particular significance for powder sterilization because of the insulating effects of the powder.

[11] See Appendix III for discussion of certain biologic components that are aseptically handled from the start of the process.

[11] 参照附录 III，关于从加工开始就无菌处理的某些生物制品成分的讨论。

干热灭菌对于那些热稳定且不可溶解的成分是一个合适的方法。然而，由于粉末的绝热性能，在对粉末灭菌时，仔细研究热穿透及热分布状况很重要。

Irradiation can be used to sterilize some components. Studies should be conducted to demonstrate that the process is appropriate for the component.

放射也可用于某些成分的灭菌。应当进行研究，证明放射对这种成分的适用性。

B. Containers/Closures
容器/密封

1. Preparation
准备

Containers and closures should be rendered sterile and, for parenteral drug products, nonpyrogenic. The process used will depend primarily on the nature of the container and/or closure materials. The validation study for such a process should be adequate to demonstrate its ability to render materials sterile and non-pyrogenic. Written procedures should specify the frequency of revalidation of these processes as well as time limits for holding sterile, depyrogenated containers and closures.

容器和密封应当灭菌，并且对于注射用药，应当除热源。使用的工艺将主要由容器和/或密封的材料性质决定。这个工艺的验证研究应当足以证明它足以进行物料的灭菌和除热源。应当用书面程序来限定这些程序的再验证频率，以及保存无菌无热源的容器和密封的有效期。

Pre-sterilization preparation of glass containers usually involves a series of wash and rinse cycles. These cycles serve an important role in removing foreign matter. We recommend use of rinse water of high purity so as not to contaminate containers. For parenteral products, final rinse water should meet the specifications of WFI, USP.

玻璃容器的消毒前准备通常包括一系列的清洗和冲淋程序。这些冲洗对洗掉外来的杂质很重要。我们建议用高度纯净的水冲洗，这样不会污染容器。对于注射用药，最后一道冲淋水应当符合 USP 的注射用水的要求。

The adequacy of the depyrogenation process can be assessed by spiking containers and closures with known quantities of endotoxin, followed by measuring endotoxin content after depyrogenation. The challenge studies can generally be performed by directly applying a reconstituted endotoxin solution onto the surfaces being tested. The endotoxin solution should then be allowed to air dry. Positive controls should be used to measure the percentage of endotoxin recovery by the test method. Validation study data should demonstrate that the process reduces the endotoxin content by at least 99.9 percent (3 logs) (see Section VII).[12]

除热源程序的效果可以通过如下方法评估：将已知量的内毒素喷到容器和密封上，除热源过程结束后再测定残留的内毒素量。挑战实验可以通过将重新溶解的内毒素溶液直接加到被测试物质的表面。让内毒素溶液自然风干。阳性对照用来测试实验方法的内毒素的回收率。验证研究数据应当能规定这个过程降低的内毒素含量至少 99.9%（10 的三次方）（请看第 7 章）。[12]

[12] When this level of depyrogenation by dry heat has been successfully validated using endotoxin challenge, a sterilization validation using a biological indicator challenge would not be indicated.

[12] 当使用内毒素挑战成功验证干热处理已经达到该除热原标准时，不用采取生物指示剂的灭菌验证。

Subjecting glass containers to dry heat generally accomplishes both sterilization and depyrogenation. Validation of dry heat sterilization and depyrogenation should include appropriate heat distribution and penetration studies as well as the use of worst-case process cycles, container characteristics (e.g., mass), and specific loading configurations to represent actual production runs. See Section IX.C. Plastic containers used for parenteral products also should be non-pyrogenic. Where applicable, multiple WFI rinses can be effective in removing pyrogens from these containers.

玻璃容器进行干热能实现灭菌和除热原两个目的。干热灭菌及除热原的验证应当包括适当的热分布、热穿透研究、以及最差状况的运行、容器性质（如：体积很大）以及特定的模拟实际生产状况的装载模式。请看第 9 章 C。用于注射用药的塑料容器也应当是无热源的。在使用时，大量注射用水冲洗能有效去除容器上的热原。

Plastic containers can be sterilized with an appropriate gas, irradiation, or other suitable means. For gases such as Ethylene Oxide (EtO), certain issues should receive attention. For example, the parameters and limits of the EtO sterilization cycle (e.g., temperature, pressure, humidity, gas concentration, exposure time, degassing, aeration, and determination of residuals) should be specified and monitored closely. EtO is an effective surface sterilant and is also used to penetrate certain packages with porous overwrapping. Biological indicators are of special importance in demonstrating the effectiveness of EtO and other gas sterilization processes. We recommend that these methods be carefully controlled and validated to evaluate whether consistent penetration of the sterilant can be achieved and to minimize residuals. Residuals from EtO processes typically include ethylene oxide as well as its byproducts, and should be within specified limits.

塑料容器可以用合适的气体、放射或其他适当的方法来灭菌。有些气体象环氧乙烷，应当注意一些使用事项。比如：应当设定环氧乙烷灭菌的参数和限制（如：温度、压力、湿度、气体浓度、暴露时间、气体散发、通风和残留浓度的确认）并严密监控。环氧乙烷是一种有效的表面杀菌剂，也能用于多孔织物包装的包裹的灭菌。生物指示剂在证明环氧乙烷和其他气体灭菌的有效性上特别重要。我们建议小心控制和验证这些方法，以判断杀菌气体能否渗透以及尽可能减少残留。环氧乙烷灭菌过程的残留物质，包括环氧乙烷和它的副产品，应当在设定的控制范围内。

Rubber closures (e.g., stoppers and syringe plungers) can be cleaned by multiple cycles of washing and rinsing prior to final steam or irradiation sterilization. At minimum, the initial rinses for the washing process should employ at least Purified Water, USP, of minimal endotoxin content, followed by final rinse(s) with WFI for parenteral products. Normally, depyrogenation can be achieved by multiple rinses of hot WFI. The time between washing, drying (where appropriate), and sterilizing should be minimized because residual moisture on the stoppers can support microbial growth and the generation of endotoxins. Because rubber is a poor conductor of heat, extra attention is indicated in the validation of processes that use heat with respect to its penetration into the rubber stopper load (See Section IX.C). Validation data from the washing procedure should demonstrate successful endotoxin removal from rubber materials.

橡胶密封（如：胶塞及注射器活塞）可以在最后蒸气或放射灭菌前，进行多次的清洗和冲淋。最初的冲洗至少要用美国药典所规定的纯化水（有最少的内毒素含量），最后用注射用水来冲洗。通常，除热原可以通过用热的注射用水的多次冲洗来实现。在冲洗，干燥（适当时）和灭菌之间的时间 应当减到最少，因为胶塞上的残留湿气可以造成微生物的生长以及内毒素的产生。由于橡胶是热的不良导体，验证过程应当特别注意热力灭菌胶塞时热的穿透过程（请看第 9 章 C）。冲洗过程的验证数据应当能够证明橡胶物质中内毒素已被成功去除。

A potential source of contamination is the siliconization of rubber stoppers. Silicone used in the preparation of rubber stoppers should meet appropriate quality control criteria and not have an adverse effect on the safety, quality, or purity of the drug product.

一个潜在的污染来源是胶塞的硅化过程。生产胶塞的原料也应符合恰当的质量控制标准，对药品的安全、质量和纯度不会产生负面影响。

Contract facilities that perform sterilization and/or depyrogenation of containers and closures are subject to the same CGMP requirements as those established for in-house processing. The finished dosage form manufacturer should review and assess the contractor's validation protocol and final validation report. In accord with 211.84(d)(3), a manufacturer who establishes the reliability of the supplier’s test results at appropriate intervals may accept containers or closures based on visual identification and Certificate of Analysis review.

如同现场进行灭菌和/或除热源过程，合同执行容器和密封的灭菌和/或除热源的厂家也应当符合 cGMP 的要求。药品成品生产商应当审核和评估合同方的最终验证大纲和报告。根据 CFR 的 211.84(d)(3)，建立了定期确认供应商测试结果的可靠性的生产商，可以根据目测和分析测试报告审核，接受容器和密封物。

2. Inspection of Container Closure System
容器密封系统的检查

A container closure system that permits penetration of microorganisms is unsuitable for a sterile product. Any damaged or defective units should be detected, and removed, during inspection of the final sealed product. Safeguards should be implemented to strictly preclude shipment of product that may lack container closure integrity and lead to nonsterility. Equipment suitability problems or incoming container or closure deficiencies can cause loss of container closure system integrity. For example, failure to detect vials fractured by faulty machinery as well as by mishandling of bulk finished stock has led to drug recalls. If damage that is not readily detected leads to loss of container closure integrity, improved procedures should be rapidly implemented to prevent and detect such defects.

一个能容许微生物渗透的密封系统对无菌产品是不合适的。在检查最后密封产品时，应当查出和去除任何有损坏或有缺陷的产品。采取安全措施，严格预防那些容器密封不好、导致无菌性受破坏的产品发货。设备适用性问题或买进的容器和密封物有缺陷会使容器丧失密封性。比如：由于机器故障或半成品处理不当造成漏检破损的小瓶，曾经引起产品的召

回。如果不容易检出的容器破损导致容器密封完整性受到破坏，应当尽快实施改进措施来预防和检出这类破损。

Functional defects in delivery devices (e.g., syringe device defects, delivery volume) can also result in product quality problems and should be monitored by appropriate in-process testing.

传递装置有功能性缺陷时（如：注射装置有问题，注射量）也可能导致产品质量问题，应当采用恰当的在线检测措施。

Any defects or results outside the specifications established for in-process and final inspection are to be investigated in accord with §211.192.

根据 CFR 211.192 调查超出工艺中检查和成品检查既定规格的任何缺陷或结果。

VII. ENDOTOXIN CONTROL
内毒素控制

21 CFR 211.63 states that "Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance."

CFR211.63 规定，"用于生产，加工，包装或配制的药品应当有恰当的设计，足够大小，而且恰当地位于方便操作的地方，以便使用，清洁和维护。"

21 CFR 211.65(a) states that "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

CFR 211.65(a)规定，"设备的装置应当能使接触成分，在生产材料，或药品的表面应当没有反应性、附加性或吸附性，因为这会改变药品的安全、成分、浓度、质量或纯度，使之超出官方或其它规定的要求。"

21 CFR 211.67(a) states that "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identify, strength, quality, or purity of the drug product beyond the official or other established requirements."

CFR211..67(a)规定，"设备和器具应当定时清洗，维护和消毒，以防故障及感染，这会感染药品的因为这会改变药品的安全、成分、浓度、质量或纯度，使之超出官方或其它规定的要求。"

21 CFR 211.94(c) states that "Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use."

CFR211.94(c)规定，"药品的包装和密封应当干净，由于药品的性质决定，应当消毒、加工、去除热原成分，以实现包装的功能。"

21 CFR 211.167(a) states that "For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed."

CFR211.167(a)规定"对每一批无菌和/或无热原药品，应当有恰当的实验室测验，使之符合这些要求。测验程序应当是书面的，也应当跟踪。"

Endotoxin contamination of an injectable product can occur as a result of poor CGMP controls. Certain patient populations (e.g., neonates), those receiving other injections concomitantly, or those administered a parenteral in atypically large volumes or doses can be at greater risk for pyrogenic reaction than anticipated by the established limits based on body weight of a normal healthy adult (Ref. 6, 7). Such clinical concerns reinforce the importance of exercising appropriate CGMP controls to prevent generation of endotoxins. Drug product components, containers, closures, storage time limitations, and manufacturing equipment are among the areas to address in establishing endotoxin control.

注射药品的内毒素感染可能是 cGMP 控制不当的结果。因为内毒素限度是根据普通人的身体重量规定的，所以某些患者群体（如：初生婴儿）、那些同时注射其它药物的人、或

那些大量注射的人，由于高热反应所带来的危险，可能会比用一个普通人大的多。这些临床问题强调了加强 cGMP 控制、防止内毒素产生的重要性。药品成分、容器、密封、储存、时间限制、生产设备是需要控制内毒素的范围。

Adequate cleaning, drying, and storage of equipment will control bioburden and prevent contribution of endotoxin load. Equipment should be designed to be easily assembled and disassembled, cleaned, sanitized, and/or sterilized. If adequate procedures are not employed, endotoxins can be contributed by both upstream and downstream processing equipment.

充分的清洗、干燥及设备储存会控制生物负荷，防止内毒素的产生。设备的设计应当易于装卸、清洗和/或消毒。如果不采取足够的行动，内毒素可能由工艺设备的上下游产生。

Sterilizing-grade filters and moist heat sterilization have not been shown to be effective in removing endotoxin. Endotoxin on equipment surfaces can be inactivated by high-temperature dry heat, or removed from equipment surfaces by cleaning procedures. Some clean-in-place procedures employ initial rinses with appropriate high purity water and/or a cleaning agent (e.g., acid, base, surfactant), followed by final rinses with heated WFI. Equipment should be dried following cleaning, unless the equipment proceeds immediately to the sterilization step.

已经证明除菌级滤器和湿热消毒不能有效去除内毒素。设备表面的内毒素可以用高温干热失活，或用清洗程序从设备表面去除。一些原位清洗程序用高纯净的水及清洁剂（如：酸、碱、表面活性剂），然后用加热的注射用水冲洗。在清洗后设备应当干燥，除非消毒后马上要使用此设备。

VIII. TIME LIMITATIONS
时间限制

21 CFR 211.111 states that "When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented."

CFR211.111 规定，"应当建立完成每个生产步骤的时间限制，以确保药品的质量。在不危及药品质量的情况下，从规定时间限制的偏差是可以接受的。这种偏差必须确认并存档。"

When appropriate, time limits must be established for each phase of aseptic processing (§211.111). Time limits should include, for example, the period between the start of bulk product compounding and its sterilization, filtration processes, product exposure while on the processing line, and storage of sterilized equipment, containers and closures. The time limits established for the various production phases should be supported by data. Bioburden and endotoxin load should be assessed when establishing time limits for stages such as the formulation processing stage.

通常，无菌加工的每个步骤必须有时间限制（§211.111）。时间限制应当包括：比如：从批药品混合开始到消毒的时间、各步过滤之间的时间、在生产线上的产品暴露时间、设备、容器和密封灭菌后的时间。在不同生产过程中的时间限制应当有数据支持。在建立例如配方生产过程的时间限制时，应当测定生物负荷和内毒素载量。

The total time for product filtration should be limited to an established maximum to prevent microorganisms from penetrating the filter. Such a time limit should also prevent a significant increase in upstream bioburden and endotoxin load. Because they can provide a substrate for microbial attachment, maximum use times for those filters used upstream for solution clarification or particle removal should also be established and justified.

产品过滤的总时间不应超过防止微生物渗透滤器的最长时间。这样的时限应当也阻止上游生物负荷和内毒素载量的明显增加。因为用于上游溶液澄清或去除微粒的滤器能成为微生物附着的培养基，所以也应当建立和确认它们的最长使用时间。

IX. VALIDATION OF ASEPTIC PROCESSING AND STERILIZATION
无菌加工和灭菌的验证

21 CFR 211.63, 211.65, and 211.67 address, respectively, "Equipment design, size, and location," "Equipment construction," and "Equipment cleaning and maintenance."

CFR 211.63, 211.65 及 211.67 分别规定“设备设计、尺寸和位置”；“设备构造”；“设备清洗和维护”。

21 CFR 211.84(c) states, in part, that "Samples shall be collected in accordance with the following procedures: * * * (3) Sterile equipment and aseptic sampling techniques shall be used when necessary."

CFR 211.84（c) 部分规定，“应当按照下面程序收集样品：…(3)在必要时，应当使用无菌设备和无菌取样技术。”

21 CFR 211.100(a) states, in part, that "There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart * * *."

CFR 211.1..(a)部分规定，“应当有生产和工艺控制的书面程序，所述程序设计用于保证产品具有其应该具有的成分、浓度、质量和纯度。所述程序应当包括在该亚部分内的所有要求…。”

21 CFR 211.113(b) states that "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."

CFR 211.113(b)规定，“应当建立和遵从设计用于预防无菌药品受到微生物污染的合适书面程序。所述程序应当包括验证任何灭菌工艺。”

This section primarily discusses routine qualification and validation study recommendations. Change control procedures are addressed only briefly, but are an important part of the quality systems established by a firm. A change in facility, equipment, process, or test method should be evaluated through the written change control program, triggering an evaluation of the need for revalidation or requalification.

本部分主要讨论常规确认和验证研究推荐。变更控制程序在这里仅简要讨论，但却是企业建立的质量系统的重要部分。厂房、设备、工艺或测试方法的变更应当通过书面变更控制程序进行评估，并评估再验证或再确认的需要。

A. Process Simulations
过程模拟

To ensure the sterility of products purporting to be sterile, sterilization, aseptic filling and closing operations must be adequately validated (§211.113). The goal of even the most effective sterilization processes can be defeated if the sterilized elements of a product (the drug formulation, the container, and the closure) are brought together under conditions that contaminate any of those elements.

为保证无菌产品的无菌性，必须充分验证灭菌、无菌分装和封口操作(§211.113)。如果产品的已灭菌元件(药物制剂、容器和密封)组合在一起的条件可能污染其中任何一种元件，那么上游最有效的灭菌工艺都将白费。

An aseptic processing operation should be validated using a microbiological growth medium in place of the product. This *process simulation,* also known as a *media fill,* normally includes exposing the microbiological growth medium to product contact surfaces of equipment, container closure systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo. The sealed containers filled with the medium are then incubated to detect microbial contamination. Results are then interpreted to assess the potential for a unit of drug product to become contaminated during actual operations (e.g., start-up, sterile ingredient additions, aseptic connections, filling, closing). Environmental monitoring data from the process simulation can also provide useful information for the processing line evaluation.

应当使用微生物培养基代替产品进行无菌加工操作的验证。这个过程模拟，也叫培养基罐装，通常包括使所述微生物培养基暴露在产品接触的设备表面、容器密封系统、关键区域和加工操作，以充分模拟产品本身可能会经历的同样暴露。 然后培养装有培养基的封口容器，检测微生物污染。然后解释结果，评估单位药品在实际操作过程中受到污染的可能性(如开机、添加无菌成分、无菌连接、分装、封口)。来自工艺模拟的环境监测数据也为评估工艺流程提供有用的信息。

1. Study Design
研究设计

A media fill program should incorporate the contamination risk factors that occur on a production line, and accurately assesses the state of process control. Media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations. FDA recommends that the media fill program address applicable issues such as:

培养基罐装程序应该加入在生产线上出现的污染风险因素，并准确评价工艺控制的状态。培养基罐装研究应该最接近地模拟无菌生产操作，并根据情况加入最差情况和条件，以挑战无菌操作。FDA 建议培养基罐封程序加入可模拟的情况，例如：

- Factors associated with the longest permitted run on the processing line that can pose contamination risk (e.g., operator fatigue)

  与在生产线上最长允许时间有关的因素，这种因素会造成污染风险（如： 操作员疲惫）

- Representative number, type, and complexity of normal interventions that occur with each run, as well as nonroutine interventions and events (e.g., maintenance, stoppages, equipment adjustments)

每次运行出现的正常干预的有代表性数量、类型和复杂性，以及非常规的干预和事件(如维护、暂停、设备调整)

- Lyophilization, when applicable

  冻干法，在适用的时候

- Aseptic assembly of equipment (e.g., at start-up, during processing)

  设备无菌组装（如：操作开机时）

- Number of personnel and their activities

  人员数量和他们的活动

- Representative number of aseptic additions (e.g., charging containers and closures as well as sterile ingredients) or transfers

  无菌添加（如：装载容器和密封物以及无菌成分）或转移，以能够代表实际生产的数量

- Shift changes, breaks, and gown changes (when applicable)

  轮班、休息、及换工作服（适当的时候）

- Type of aseptic equipment disconnections/connections

  无菌设备断开/连接的类型

- Aseptic sample collections

  无菌采样

- Line speed and configuration

  生产线速度和构造

- Weight checks

  重量检查

- Container closure systems (e.g., sizes, type, compatibility with equipment)

  容器密封系统（如：尺寸，类型、与设备的兼容性）

- Specific provisions in written procedures relating to aseptic processing (e.g., conditions permitted before line clearance is mandated)

  与无菌加工相关的具体书面规定（如： 在清场前允许的条件）

A written batch record, documenting production conditions and simulated activities, should be prepared for each media fill run. The same vigilance should be observed in both media fill and routine production runs. The firm's rationale for the conditions and activities simulated during the media fill should be clearly defined. Media fills should not be used to justify practices that pose unnecessary contamination risks.

每次培养基罐装试验都应该有书面的批记录，其中记录生产条件和所模拟的活动。培养基罐装批和常规生产批应当有同样的无菌警觉性。企业应当清楚定义在培养基罐装期间所模拟条件和活动的基本原理。培养基罐装试验不能用于支持造成不必要污染风险的活动。

2. Frequency and Number of Runs
试验频率和数量

When a processing line is initially qualified, individual media fills should be repeated enough times to ensure that results are consistent and meaningful. This approach is important because a single run can be inconclusive, while multiple runs with divergent results signal a process that is not in control. We recommend that at least three consecutive separate successful runs be performed during initial line qualification. Subsequently, routine semi-annual qualification conducted for each processing line will evaluate the state of control of the aseptic process. Activities and interventions representative of each shift, and shift changeover, should be incorporated into the design of the semi-annual qualification program. For example, the evaluation of a production shift should address its unique time-related and operational features.[13] All personnel who are authorized to enter the aseptic processing room during manufacturing, including technicians and maintenance personnel, should participate in a media fill at least once a year. Participation should be consistent with the nature of each operator's duties during routine production.

当最初验证生产线时，各个培养基罐装试验应当重复足够次数，以保证结果是一致并且有意义的。这种方法很重要，因为单次运行无法作为决定性证据，而多次运行出现不同结果则显示工艺不受控制。我们建议在第一次生产线确认期间， 至少进行 3 次连续的成功运行。随后，每一条生产线每半年进行一次常规确认，由此评估对无菌工艺的控制。在每半年一次的确认程序中，应该加入每一班典型的活动和干预，以及换班的情况。例如，对生产班次的评估应该确认其独特的时间相关性和操作特征。[13]所有在生产期间有权进入无菌加工室的人员，包括技术和维护人员，都应当至少每年一次参加培养基灌装试验。参与程度应当与每名操作者在常规生产中的职责相一致。

Each change to a product or line change should be evaluated using a written change control system. Any changes or events that have the potential to affect the ability of the aseptic process to exclude contamination from the sterilized product should be assessed through additional media fills. For example, facility and equipment modifications, line configuration changes, significant changes in personnel, anomalies in environmental testing results, container closure system changes, extended shutdowns, or end product sterility testing showing contaminated products may be cause for revalidation of the system.

应当使用已经成文的变更控制系统评估产品或生产线的每一个变更。对于有可能影响无菌加工工艺防止无菌产品受污染的能力的任何变更或事件，都应当通过培养基灌装试验进行评估。比如： 仪器和设备的调整、生产线结构的改变、人员的重大调整、异常环境测试

[13] One example might be the movement of personnel into and out of the aseptic processing and gowning change rooms during a shift change.

[13] 一个例子是在换班时，人员进出无菌加工室和更衣室的活动。

结果、容器密封系统的改变、时间较长的停顿、或成品无菌测试显示产品受污染，这些都有可能需要系统再验证。

When data from a media fill indicate the process may not be in control, an investigation should be conducted to determine the origin of the contamination and the scope of the problem. Once corrections are instituted, process simulation run(s) should be performed to confirm that deficiencies have been corrected and the process has returned to a state of control. When an investigation fails to reach well-supported, substantive conclusions as to the cause of the media fill failure, three consecutive successful runs in tandem with increased scrutiny of the production process may be warranted.

如果培养基灌装数据显示工艺不受控制，那么应该进行调查，确定污染的来源以及问题的范围。一旦实施纠正措施，应当进行工艺模拟运行，确认已经纠正缺陷，并且工艺回到受控状态。当调查无法就培养基灌装试验失败的原因找到有数据支持并且切实合理的结论，可以用更严格的生产工艺标准进行三次连续成功的运行。

3. Duration of Runs
运行时间

The duration of aseptic processing operations is a major consideration in media fill design. Although the most accurate simulation model would be the full batch size and duration because it most closely simulates the actual production operations, other appropriate models can be justified. The duration of the media fill run should be determined by the time it takes to incorporate manipulations and interventions, as well as appropriate consideration of the duration of the actual aseptic processing operation. Interventions that commonly occur should be routinely simulated, while those occurring rarely can be simulated periodically.

无菌加工操作的时间长度是无菌灌装试验设计中的一个重要因素。尽管最准确的模拟模型是全批量和全时间长度模拟，因为这最接近地模拟了实际生产操作，但也可以使用其它合适模型。培养基灌装试验运行的时间长度应当根据以下因素确定：加入操作和干预所需的时间，以及合理考虑实际无菌加工操作的时间长度。一般情况下会出现的干预应当作为例行模拟项目，而很少出现的干预应当定期模拟。

While conventional manufacturing lines are usually automated, operated at relatively high speeds, and designed to limit operator intervention, some processes still include considerable operator involvement. When aseptic processing employs manual filling or closing, or extensive manual manipulations, the duration of the process simulation should generally be no less than the length of the actual manufacturing process to best simulate contamination risks posed by operators.

虽然通常的生产线都是自动控制，高速运转，而且在设计上减少和限制人员的干预，但一些工艺仍然包括相当数量的操作人员干预。如果无菌加工使用手工分装或密封，或大量的手工操作，那么工艺模拟时间一般不能少于实际生产时间，这样可以最佳模拟由操作员带来的污染危险。

For lyophilization operations, FDA recommends that unsealed containers be exposed to partial evacuation of the chamber in a manner that simulates the process. Vials should not be frozen, and precautions should be taken that ensure that the medium remains in an aerobic state to avoid potentially inhibiting the growth of microorganisms.

对于冻干工艺，FDA 建议在模拟工艺的条件下，把未封口的容器暴露在部分打开的冻干室内。不应冻结小管，并注意维持培养基处于有氧状态，以避免出现有可能抑制微生物生长的情况。

4. Size of Runs
批量

The simulation run sizes should be adequate to mimic commercial production conditions and accurately assess the potential for commercial batch contamination. The number of units filled during the process simulation should be based on contamination risk for a given process and sufficient to accurately simulate activities that are representative of the manufacturing process. A generally acceptable starting point for run size is in the range of 5,000 to 10,000 units. For operations with production sizes under 5,000, the number of media filled units should at least equal the maximum batch size made on the processing line (Ref. 8).

模拟批规模应当足够以模拟规模生产条件，并且能够准确评估规模生产批次污染的可能。在工艺模拟过程中罐装的批单位数量应当基于给定工艺的污染风险，并足以准确模拟生产过程中典型的活动。普遍可接受的最低批量在 5000 到 10,000 单位之间。对于批量在 5,000 单位以下的操作，培养基罐装单位的数量应当至少等于生产线上的最大批量(参考文献 8)。

When the possibility of contamination is higher based on the process design (e.g., manually intensive filling lines), a larger number of units, generally at or approaching the full production batch size, should be used. In contrast, a process conducted in an isolator (see Appendix 1) can have a low risk of contamination because of the lack of direct human intervention and can be simulated with a lower number of units as a proportion of the overall operation.

如果根据工艺设计，污染的可能性比较高（如有大量的手工分装操作），那么应该使用达到或接近全批量的单位数量。与此相比，由于没有直接的人员干预，在隔离装置(见附件 1)内进行的工艺受到污染的风险低，因此模拟可以使用比总批量更低的单位数量。

Media fill size is an especially important consideration because some batches are produced over multiple shifts or yield an unusually large number of units. These factors should be carefully evaluated when designing the simulation to adequately encompass conditions and any potential risks associated with the larger operation.

培养基灌装试验的批量是非常重要的考虑因素，因为一些批次由多个班次生产，或者产生非常大量的单位。在设计模拟试验时，应当仔细衡量这些因素，以充分包括与大规模操作有关部门的各种情况和任何潜在风险。

5. Line Speed
生产线速度

The media fill program should adequately address the range of line speeds employed during production. Each media fill run should evaluate a single line speed, and the speed chosen should be justified. For example, use of high line speed is often most appropriate in the evaluation of manufacturing processes characterized by frequent interventions or a significant degree of manual manipulation. Use of slow line speed is generally appropriate for evaluating manufacturing processes with prolonged exposure of the sterile drug product and containers/closures in the aseptic area.

培养基分装程序应当足够考虑生产过程中使用的生产线速度范围。每次培养基灌装运行应当只评估一种生产线速度，而所选择的速度应当合适。例如，高生产线速度通常最适于评价存在频繁干预和相当程度手工操作的生产工艺。低生产线速度通常适于评价无菌药品和容器/密封在无菌区域内暴露时间长的生产工艺。

6. Environmental Conditions
环境质量

Media fills should be adequately representative of the conditions under which actual manufacturing operations are conducted. An inaccurate assessment (making the process appear cleaner than it actually is) can result from conducting a media fill under extraordinary air particulate and microbial quality, or under production controls and precautions taken in preparation for the media fill. To the extent standard operating procedures permit stressful conditions (e.g., maximum number of personnel present and elevated activity level), it is important that media fills include analogous challenges to support the validity of these studies. Stressful conditions do not include artificially created environmental extremes, such as reconfiguration of HVAC systems to operate at worst-case limits.

培养基罐装应当足以代表实际生产工艺操作时的条件。在特别高的空气颗粒和微生物质量的条件下进行培养基罐装试验，或者对于培养基灌装试验采取生产控制和预防措施，有可能导致不准确的评估(使工艺看起来比实际更清洁)。在某种程度上 SOP 允许最差情况(如最大数量人员和活动水平提高)，重要的是培养基灌装试验包括模拟实验以支持这些研究的有效性。最差条件不包括人为创造的极端环境，例如调整 HVAC 系统使其在最差条件下操作。

7. Media
培养基

In general, a microbiological growth medium, such as soybean casein digest medium, should be used. Use of anaerobic growth media (e.g., fluid thioglycollate medium) should be considered in special circumstances. The media selected should be demonstrated to promote growth of gram-positive and gram-negative bacteria, and yeast and mold (e.g., USP indicator organisms). The QC laboratory should determine if USP indicator organisms sufficiently represent production-related isolates. Environmental monitoring and sterility test isolates can be substituted (as appropriate) or added to the growth promotion challenge. Growth promotion units should be

inoculated with a <100 CFU challenge. If the growth promotion testing fails, the origin of any contamination found during the simulation should nonetheless be investigated and the media fill promptly repeated.[14]

一般而言，应当使用微生物培养基，例如大豆酪蛋白培养基。在特别情况下应当考虑使用厌氧生长培养基(如液体 thioglycollate 培养基)。选定培养基应当可以促进革兰氏阳性和革兰氏阴性细菌、酵母和霉菌的生长(如，美国药典中的生物指示剂)。QC 实验室应当决定 USP 生物指示剂是否足以代表与生产有关的分离物。在生长促进实验中应当取代(根据需要)或加入环境监测和无菌测试分离物。生长促进单位应当接种<100 CFU 的微生物。如果生长测试失败，应当调查在在模拟期间发现的任何污染源，并及时重复培养基罐装试验。[14]

The production process should be accurately simulated using media and conditions that optimize detection of any microbiological contamination. Each unit should be filled with an appropriate quantity and type of microbial growth medium to contact the inner container closure surfaces (when the unit is inverted or thoroughly swirled) and permit visual detection of microbial growth.

应当使用最适于检出任何微生物污染的培养基和条件，准确模拟生产工艺。
应当用合适数量和类型的微生物生长培养基灌装每个单位，使其接触容器内密封表面(倒转或完全振荡)，并允许目测检查微生物生长。

Some drug manufacturers have expressed concern over the possible contamination of the facility and equipment with nutrient media during media fill runs. However, if the medium is handled properly and is promptly followed by the cleaning, sanitizing, and, where necessary, sterilization of equipment, subsequently processed products are not likely to be compromised.

一些药品生产商担心培养基灌装试验期间的培养基可能会污染厂房和设备。然而，如果培养基处理得当，并且随后及时清洗、消毒，并在适当时对设备进行灭菌，那么随后加工的产品就不大可能受到污染。

8. Incubation and Examination of Media-Filled Units
培养基罐装单位的培养和检查

Media units should be incubated under conditions adequate to detect microorganisms that might otherwise be difficult to culture. Incubation conditions should be established in accord with the following general guidelines:

在允许以高灵敏度检出微生物的条件下培养灌装单位。培养条件应当符合下面指导：

- Incubation temperature should be suitable for recovery of bioburden and environmental isolates and should at no time be outside the range of 20-35°C. Incubation temperature should be maintained within ±2.5°C of the target temperature.

[14] The cause of the growth promotion failure should also be investigated.

[14] 也应当调查生产促进试验失败的原因。

培养温度应当适于回收生物负荷和环境分离物，并且决不应当超出 20-35°C 的范围。 培养温度应当保持在目标温度+2.5°C 的范围内。

- Incubation time should not be less than 14 days. If two temperatures are used for the incubation of the media filled units, the units should be incubated for at least 7 days at each temperature (starting with the lower temperature).

  培养时间应当不少于 14 天。如果用两个不同温度温育培养基罐装单位，那么所述单位应当在每个温度下培养至少 7 天（从较低温度开始）。

Each media-filled unit should be examined for contamination by personnel with appropriate education, training, and experience in inspecting media fill units for microbiological contamination. If QC personnel do not perform the inspection, there should be QC unit oversight throughout any such examination. All suspect units identified during the examination should be brought to the immediate attention of the QC microbiologist. To allow for visual detection of microbial growth, we recommend substituting clear containers (with otherwise identical physical properties) for amber or other opaque containers. If appropriate, other methods can also be considered to ensure visual detection.

每名检查培养基灌装单位污染的人员都应当就如何检查培养基灌装单位中的微生物污染接受合适的教育和培训，并且有足够的经验。如果 QC 人员不进行所述检查，那么 QC 部门应当监督所述检查。在整个检查过程中发现的所有有疑的单位应当立即报告 QC 微生物检查员。为允许目测检出微生物生长，我们建议用清澈的容器(其它物理性质相同)取代琥珀色和其他不透明的容器。在合适的情况下，也可以考虑其它方法来保证目测。

When a firm performs a final product inspection of units immediately following the media fill run, all integral units should proceed to incubation. Units found to have defects not related to integrity (e.g., cosmetic defect) should be incubated; units that lack integrity should be rejected. Erroneously rejected units should be returned promptly for incubation with the media fill lot.

企业在培养基灌装运行后立即进行最后产品检查，所有完整单位都送去培养。应当培养缺陷与完整性无关(如表面缺陷)的单位；拒绝完整性受到破坏的单位。被错误拒绝的单位应当及时送回并与同一培养基灌装试验批一起培养。

After incubation is underway, any unit found to be damaged should be included in the data for the media fill run, because the units can be representative of drug product released to the market. Any decision to exclude such incubated units (i.e., non-integral) from the final run tally should be fully justified and the deviation explained in the media fill report. If a correlation emerges between difficult to detect damage and microbial contamination, a thorough investigation should be conducted to determine its cause (see Section VI.B).

培养开始后，任何发现有损坏的单元应当包括在培养基罐装批数据中，因为这些单元代表可能流入市场的药品。从最终批量中排除所述培养单位(即缺乏完整性)的任何决定都应当

有证据支持并得到批准，并在培养基灌装试验报告中解释偏差。如果在难以检测破损与微生物污染之间有相关性，应该进行彻底调查以确定其原因(见部分第 6 章 B 部分)。

Written procedures regarding aseptic interventions should be clear and specific (e.g., intervention type; quantity of units removed), providing for consistent production practices and assessment of these practices during media fills. If written procedures and batch documentation are adequate to describe an associated clearance, the intervention units removed during media fills do not need to be incubated.[15] Where procedures lack specificity, there would be insufficient justification for exclusion of units removed during an intervention from incubation. For example, if a production procedure requires removal of 10 units after an intervention at the stoppering station infeed, batch records (i.e., for production and media fills) should clearly document conformance with this procedure. In no case should more units be removed during a media fill intervention than would be cleared during a production run.

有关无菌干预的书面程序应当清晰明确(如：干涉类型，移除单位的数量)，这样使生产具有连续性，并允许评估培养基灌装试验中的这些操作。如果书面程序和批文件足以描述对单位的清除，那么不需要培养在培养基灌装试验中移除的干预单位。[15] 如果程序不明确，那么在从培养的干预过程中,没有足够理由排除已移出的单位。例如，假如生产程序要求在每次对胶塞机入口进行操作后除去 10 个单位，那么批记录(即生产记录和培养基灌装试验记录)应当清楚记录与该程序的一致性。不论任何情况，在培养基灌装试验中因干预而除去的单位都不应当多于实际生产中的除去的数量。

The ability of a media fill run to detect potential contamination from a given simulated activity should not be compromised by a large-scale line clearance. We recommend incorporating appropriate study provisions to avoid and address a large line clearance that results in the removal of a unit possibly contaminated during an unrelated event or intervention.

培养基灌装试验通过模拟活动检测潜在污染的能力不应当受到大规模生产线清除的影响。我们建议加入合适的研究前提，以避免和解决大规模清除，导致除去在不相关事件或干预过程中可能受到污染的单位。

Appropriate criteria should be established for yield[16] and accountability (reconciliation of filled units). Media fill record reconciliation documentation should include a full accounting and description of units rejected from a batch.

应当建立产量[16]和可追踪性(已灌装产品的数量平衡)的合适标准。培养基罐装试验记录数量平衡的文件化应当包括该批拒绝的单位的数量和描述。

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[15] To assess contamination risks during initial aseptic setup (before fill), valuable information can be obtained by incubating all such units that may be normally removed. These units are typically incubated separately, and would not necessarily be included in the acceptance criteria for the media fill.
[15] 为了评价在首次无菌开机期间(分装前)的污染风险，可以通过培养所有这些通常被去除的单位，来获得有用的信息。这些基因通常分隔培养，不一定包含在培养基灌装试验的合格标准中。

[16] Total units incubated/total number of units filled.
[16] 总温育单位/分装单位总数。

9. Interpretation of Test Results
试验结果的解释

The process simulation run should be observed by the QC Unit, and contaminated units should be reconcilable with the approximate time and the activity being simulated during the media fill. Video recording of a media fill may serve as a useful aide in identifying personnel practices that could negatively affect the aseptic process.

QC 部门应监测工艺模拟过程，应当将受污染单位与培养基灌装试验期间所模拟的合适时间和活动对应起来。对培养基灌装试验的录像可以作为鉴定可能不利影响无菌加工的人员操作的有用工具。

Any contaminated unit should be considered objectionable and investigated. The microorganisms should be identified to species level. The investigation should survey the possible causes of contamination. In addition, any failure investigation should assess the impact on commercial drugs produced on the line since the last media fill.

任何污染单位都应当被认为是不利的，并且需要调查。污染微生物应当鉴定到物种水平。调查应当审查感染的可能原因。此外，任何失败调查都应该评估从上一次培养基灌装试验以来生产线上生产的产品受到的影响。

Whenever contamination exists in a media fill run, it should be considered indicative of a potential sterility assurance problem, regardless of run size. The number of contaminated units should not be expected to increase in a directly proportional manner with the number of vials in the media fill run. Test results should reliably and reproducibly show that the units produced by an aseptic processing operation are sterile. Modern aseptic processing operations in suitably designed facilities have demonstrated a capability of meeting contamination levels approaching zero (Ref. 8, 9) and should normally yield no media fill contamination. Recommended criteria for assessing state of aseptic line control are as follows:

不论何时培养基灌装试验中出现污染，不论批量多大，都应当认为无菌保证可能存在问题。污染单位的数量不应当与培养基灌装试验批量有直接相关关系。测试结果应当可靠并且可重复地证明：通过无菌加工操作生产的单位是无菌的。在设计合理的设施中的现代无菌加工操作已经证明, 污染水平能够接近零(参考文献 8，9)，并且通常应当不出现培养基灌装污染。评估无菌线控制状态的推荐标准如下：

- When filling fewer than 5000 units, no contaminated units should be detected.
  -- One (1) contaminated unit is considered cause for revalidation, following an investigation.

  当分装少于 5,000 单位时，不应当检出任何感染单位。
  -- 一个（1）感染单位在经过调查后，可能导致再验证。

- When filling from 5,000 to 10,000 units:

-- One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill.
-- Two (2) contaminated units are considered cause for revalidation, following investigation.

当罐装 5,000 到 10,000 个单位时：
-- 一个（1）感染单位应当导致调查，包括考虑重复培养基罐装试验。
-- 两个（2）污染单位经过调查后，可能导致再验证。

- When filling more than 10,000 units:
  -- One (1) contaminated unit should result in an investigation.
  -- Two (2) contaminated units are considered cause for revalidation, following investigation.

  当罐装多于 10,000 个单位时：
  -- 一个污染单位应当引起调查。
  -- 两个污染单位经过调查后，可能导致再验证。

For any run size, intermittent incidents of microbial contamination in media filled runs can be indicative of a persistent low-level contamination problem that should be investigated. Accordingly, recurring incidents of contaminated units in media fills for an individual line, regardless of acceptance criteria, would be a signal of an adverse trend on the aseptic processing line that should lead to problem identification, correction, and revalidation.

对于任何批量，在培养基灌装试验中间歇出现微生物污染可能是存在低水平污染问题的征兆，应当进行调查。因此，如果在一条生产线的培养基灌装试验中重复出现污染单位，那么不论合格标准如何，都是无菌加工生产线不利趋势的信号，应当导致问题鉴定、纠正和再验证。

A firm's use of media fill acceptance criteria allowing infrequent contamination does not mean that a distributed lot of drug product purporting to be sterile may contain a nonsterile unit. The purpose of an aseptic process is to prevent any contamination. A manufacturer is fully liable for the shipment of any nonsterile unit, an act that is prohibited under the FD&C Act (Section 301(a) 21 U.S.C. 331(a)). FDA also recognizes that there might be some scientific and technical limitations on how precisely and accurately process simulations can characterize a system of controls intended to exclude contamination.

一个公司如果在培养基罐装的合格标准如果允许偶然出现的感染，并不意味着销售的无菌药品可以包含非无菌单位。无菌加工的目的是预防任何感染。生产商对任何非无菌产品的售出负完全责任，违反了联邦食品，药品和化妆品法(CFR 301(a)21 U.S.C.331(a))。FDA 也认识到，对一个除菌控制系统的模拟的精确度和正确度，也许存在科学和技术的限制。

As with any process validation run, it is important to note that *invalidation* of a media fill run should be a rare occurrence. A media fill run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. Supporting documentation and justification should be provided in such cases.

对于任何工艺验证，培养基罐装失效是非常罕见的。只有在书面程序要求上市批次受到同样处理的情况下，才能否定培养基灌装试验。在这种情况下，应当提供支持文件和理由。

B. Filtration Efficacy
过滤功效

Filtration is a common method of sterilizing drug product solutions. A sterilizing grade filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent.[17] Currently, such filters usually have a rated pore size of 0.2 μm or smaller.[18] Use of redundant sterilizing filters should be considered in many cases. Whatever filter or combination of filters is used, validation should include microbiological challenges to simulate worst-case production conditions for the material to be filtered and integrity test results of the filters used for the study. Product bioburden should be evaluated when selecting a suitable challenge microorganism to assess which microorganism represents the worst-case challenge to the filter. The microorganism *Brevundimonas diminuta* (ATCC 19146) when properly grown, harvested and used, is a common challenge microorganism for 0.2 μm rated filters because of its small size (0.3 μm mean diameter). The manufacturing process controls should be designed to minimize the bioburden of the unfiltered product. Bioburden of unsterilized bulk solutions should be determined to trend the characteristics of potentially contaminating organisms.

过滤是对药品溶液进行灭菌的一种常用方法。应当验证除菌级滤器重复地从工艺流体中除去生活微生物并获得无菌物质的能力。[17]目前，这类滤器的孔径为 0.2 μm 或以下。[18]在许多情况下应当多次使用除菌滤器。无论使用何种滤器或滤器组合，验证应当包括微生物实验，模拟需要过滤的材料的最差生产条件，并且包括用于研究的滤器的完整性测试结果。当选择合适实验微生物以评估何种微生物代表需要过滤的最差实验时，应当评估产品生物负荷。缺陷短波单胞菌(Brevundimonas diminuta, ATCC 19146)在合适培养、收获和使用的情况下，是 0.2 μm 滤器通常使用的实验微生物，因为其尺寸较小(平均直径 0.3 μm)。生产过程的控制应当设计成最小化未过滤产品的生物负荷。应当测定未过滤半成品溶液的生物负荷，追踪可能污染微生物的特征。

In certain cases, when justified as equivalent or better than use of *B. diminuta*, it may be appropriate to conduct bacterial retention studies with a bioburden isolate. The number of microorganisms in the challenge is important because a filter can contain a number of pores larger than the nominal rating, which has the potential to allow passage of microorganisms. The probability of such passage is considered to increase as the number of organisms (bioburden) in the material to be filtered increases. A challenge concentration of at least 10^7 organisms per cm^2 of effective filtration area should generally be used, resulting in no passage of the challenge

[17] This document does not address virus removal.

[17] 这个文件不涉及去除病毒。

[18] 0.22μ and 0.2μ are considered interchangeable nominal pore size ratings.

[18] 0.22μ 和 0.2μ是可互换使用的名义孔径。

microorganism. The challenge concentration used for validation is intended to provide a margin of safety well beyond what would be expected in production.

在某些情况下，如果有正当理由认为某种生物负荷分离物与缺陷短波单胞菌等价或更好，那么可以用该分离物进行细菌保留研究。在实验时使用的微生物数量是重要的，因为滤器可能包含大量大于名义孔径的孔，这有可能允许微生物的通过。在要过滤的材料中生物数量(生物负荷)增加时，这种通透的可能性也增加。每 cm^2 有效过滤面积至少使用 10^7 个生物的实验浓度，并且不导致实验微生物的通透。验证使用的挑战试验浓度应当远高于生产的预期浓度，以便为生产提供良好的安全性保证。

Direct inoculation into the drug formulation is the preferred method because it provides an assessment of the effect of drug product on the filter matrix and on the challenge organism. However, directly inoculating *B. diminuta* into products with inherent bactericidal activity against this microbe, or into oil-based formulations, can lead to erroneous conclusions. When sufficiently justified, the effects of the product formulation on the membrane's integrity can be assessed using an appropriate alternate method. For example, a drug product could be filtered in a manner in which the worst-case combination of process specifications and conditions are simulated. This step could be followed by filtration of the challenge organism for a significant period of time, under the same conditions, using an appropriately modified product (e.g., lacking an antimicrobial preservative or other antimicrobial component) as the vehicle. Any divergence from a simulation using the actual product and conditions of processing should be justified.

直接接种到药品制剂是优选方法，因为这可以判定药品对于滤膜基质以及实验生物的影响。然而，将缺陷短波单胞菌直接接种进对该微生物有内在制菌活性的产品，或接种进油基制剂，可能导致错误的结论。在有足够证据支持的情况下，可以使用其它合适方法评估产品制剂对于膜完整性的影响。例如，可以在模拟工艺规格和条件最差组合的情况下，过滤药品。随后使用经过合适调整的产品(如不含抗微生物防腐剂或其它抗微生物成分)作为媒介，在同样条件下，过滤实验生物足够长的时间。在实际产品和加工条件下，与模拟过程的任何差异都应当有正当理由。

Factors that can affect filter performance generally include (1) viscosity and surface tension of the material to be filtered, (2) pH, (3) compatibility of the material or formulation components with the filter itself, (4) pressures, (5) flow rates, (6) maximum use time, (7) temperature, (8) osmolality, (9) and the effects of hydraulic shock. When designing the validation protocol, it is important to address the effect of the extremes of processing factors on the filter capability to produce sterile effluent. Filter validation should be conducted using the worst-case conditions, such as maximum filter use time and pressure (Ref. 12). Filter validation experiments, including microbial challenges, need not be conducted in the actual manufacturing areas. However, it is essential that laboratory experiments simulate actual production conditions. The specific type of filter membrane used in commercial production should be evaluated in filter validation studies. There are advantages to using production filters in these bacterial retention validation studies. When the more complex filter validation tests go beyond the capabilities of the filter user, tests are often conducted by outside laboratories or by filter manufacturers. However, it is the responsibility of the filter user to review the validation data on the efficacy of the filter in producing a sterile effluent. The data should be applicable to the user's products and conditions of use because filter performance may differ significantly for various conditions and products.

影响滤器性能的因素通常包括 (1)过滤材料的粘度和表面张力(2) pH ，(3)材料或配方成分与滤器的兼容性，(4)压力，(5)流速(6)最长使用时间，(7)温度，(8)渗透浓度和(9)液压的影响。当设计验证方案时，重要的是确定极端工艺因素对于滤器生产无菌流体的能力的影响。滤器验证应当用最差条件情况下进行，如最大滤器使用时间和压力(参考文献 12)。滤器验证试验，包括微生物实验，不一定在实际生产区域内进行。然而，实验室试验模拟真实生产条件是很有必要的。在滤器验证研究中应当评估规模生产中使用的滤膜特定类型。在这些细菌保留验证研究中，使用生产滤器是有优势的。当更为复杂的滤器验证测试超过滤器使用者的能力时，这些测试通常在外面的实验室进行，或由滤器生产商进行。但是，滤器使用者有责任审核验证数据，检查滤器生产无菌流体的功效。数据应当适用于使用者的产品和使用条件，因为滤器性能可能因不同的条件和产品而有很大差异。

After a filtration process is properly validated for a given product, process, and filter, it is important to ensure that identical filters (e.g., of identical polymer construction and pore size rating) are used in production runs. Sterilizing filters should be routinely discarded after processing of a single lot. However, in those instances when repeated use can be justified, the sterile filter validation should incorporate the maximum number of lots to be processed. Integrity testing of the filter(s) can be performed prior to processing, and should be routinely performed post-use. It is important that integrity testing be conducted after filtration to detect any filter leaks or perforations that might have occurred during the filtration. *Forward flow and bubble point* tests, when appropriately employed, are two integrity tests that can be used. A production filter's integrity test specification should be consistent with data generated during bacterial retention validation studies.

当就给定产品、工艺和滤器合适地验证过滤工艺后，重要的是保证在生产中使用同样滤器(如，同样聚合物构造和孔径)。在每一单批处理后，除菌滤器通常应当丢弃。但是，有些情况下如果有正当理由可以重复使用滤器，那么无菌滤器验证应当包括加工的最大批数。滤器的完整性测试可以在加工之前进行，也应当在使用之后定期进行。在过滤后进行完整性测试是很重要的，这可以检查出过滤过程中可能出现的任何滤器泄漏或穿孔。*Forward flow 和起泡点*测试，在使用恰当时，是两种可以使用的完整性测试方法。生产用滤器完整性测试规格应当与在细菌保留验证研究中产生的数据一致。

C. Sterilization of Equipment, Containers, and Closures
设备、容器和密封的灭菌

Equipment surfaces that contact sterilized drug product or its sterilized containers or closures must be sterile so as not to alter purity of the drug (211.67 and 211.113). Where reasonable contamination potential exists, surfaces that are in the vicinity of the sterile product should also be rendered free of viable organisms. It is as important in aseptic processing to validate the processes used to sterilize such critical equipment as it is to validate processes used to sterilize the drug product and its container and closure. Moist heat and dry heat sterilization, the most widely used, are the primary processes discussed in this document. However, many of the heat sterilization principles discussed in this guidance are also applicable to other sterilization methods.

接触灭菌后药品或其灭菌后容器或密封的设备表面必须是无菌的，这样不会改变药品的纯度(211.67 和 211.113)。当预期存在污染可能时，在无菌药品附近的表面也应当接受处理，使其没有生活微生物。在无菌加工中，验证用于灭菌所需关键设备的工艺与验证用于灭菌药品及其容器和密封同样重要。本指南讨论的主要工艺是最广泛使用的湿热灭菌和干热灭菌。但是，在本指南中讨论的许多干热灭菌原理也适用于其它灭菌方法。

Sterility of aseptic processing equipment should normally be maintained by sterilization between each batch.[19] Following sterilization, transportation and assembly of equipment, containers, and closures should be performed with strict adherence to aseptic methods in a manner that protects and sustains the product's sterile state.

通常通过每一批之间的灭菌，维持无菌加工设备的无菌性。[19]灭菌后，用严格符合无菌方法的方式，进行设备、容器和密封的灭菌、运输和装配，以保护和维持产品的无菌状态。

1. Qualification and Validation
确认和验证

Validation studies should be conducted to demonstrate the efficacy of the sterilization cycle. Requalification studies should also be performed on a periodic basis. The specific load configurations, as well as biological indicator and temperature sensor locations, should be documented in validation records. Batch production records should subsequently document adherence to the validated load patterns.

应当进行验证研究，证明灭菌循环的功效。应当定期进行再确认研究。各种装载方式、生物指示剂和温度探头的位置都应当记录在验证记录中。批生产记录应当随后记载与已验证装载方式的符合性。

It is important to remove air from the autoclave chamber as part of a steam sterilization cycle. The insulating properties of air interfere with the ability of steam to transfer its energy to the load, achieving lower lethality than associated with saturated steam. It also should be noted that the resistance of microorganisms can vary widely depending on the material to be sterilized. For this reason, careful consideration should be given during sterilization validation to the nature or type of material chosen as the carrier of the biological indicator to ensure an appropriately representative study.

在蒸汽灭菌循环中，从高压蒸汽灭菌柜移除空气是重要的。空气的绝缘性质干扰蒸汽传递能量到装载物的能力，使致死力比饱和蒸汽更低。同时应该注意到，微生物的抗性可能根据需要灭菌的材料而有很大不同。由于这个原因，在灭菌验证时，应当仔细选择作为生物指示器载体的材料的性质和类型，以保证合格、有代表性的研究。

[19] If appropriate, alternate intervals can be defined, justified, and supported by validation studies.

[19] 如果恰当， 可以用验证研究确定、证明和支持其它间隔时间。

Potentially difficult to reach locations within the sterilizer load or equipment train (for SIP applications) should be evaluated. For example, filter installations in piping can cause a substantial pressure differential across the filter, resulting in a significant temperature drop on the downstream side. We recommend placing biological indicators at appropriate downstream locations of the filter.

应当评估灭菌柜载量或设备链内(对于 SIP 应用)可能难以达到的位置。比如：管道内滤器安装可能导致滤器两边的明显压差，导致下游区温度的显著下降。我们建议在滤器下游的合适位置放置生物指示器。

Empty chamber studies evaluate numerous locations throughout a sterilizing unit (e.g., steam autoclave, dry heat oven) or equipment train (e.g., large tanks, immobile piping) to confirm uniformity of conditions (e.g., temperature, pressure). These uniformity or *mapping* studies should be conducted with calibrated measurement devices.

空载研究评估灭菌单位(如高压蒸汽灭菌柜、干热烘箱)或设备链(如大罐、固定管线)内的不同位置，确认条件的一致性(如温度、压力)。应当用经过验证的测量装置进行这些一致性或作图研究。

Heat penetration studies should be performed using the established sterilizer loads. Validation of the sterilization process with a loaded chamber demonstrates the effects of loading on thermal input to the items being sterilized and may identify difficult to heat or penetrate items where there could be insufficient lethality to attain sterility. The placement of biological indicators at numerous positions in the load, including the most difficult to sterilize places, is a direct means of confirming the efficacy of any sterilization procedure. In general, the biological indicator should be placed adjacent to the temperature sensor so as to assess the correlation between microbial lethality and predicted lethality based on thermal input. When determining which articles are difficult to sterilize, special attention should be given to the sterilization of filters, filling manifolds, and pumps. Some other examples include certain locations of tightly wrapped or densely packed supplies, securely fastened load articles, lengthy tubing, the sterile filter apparatus, hydrophobic filters, and stopper load.

应当用已经建立的灭菌器装载模式进行热穿透研究。对使用一定装载的室的灭菌工艺的验证证明装载模式对于热进入灭菌物品的影响，并可以发现难以加热或穿透的物品，这些物品的致死率可能不足以达到无菌性。在装载方式的不同位置安放生物指示器，包括在最难以灭菌的地方，是确认任何程序功效的直接方法。一般地说，生物指示器应当放在临近温度探头的地方，这样可以测量微生物致死率和根据热输入预测的微生物致死率之间的关系。在决定哪些物品难以灭菌时，应当特别注意滤器、分装管和泵的灭菌。其它例子包括紧密包装的供应材料、紧紧扎起来的装载物品、特别长的管线、无菌过滤装置、疏水滤器和胶塞。

Ultimately, cycle specifications for such sterilization methods should be based on the delivery of adequate lethality to the slowest to heat locations. A sterility assurance level of 10^{-6} or better should be demonstrated for a sterilization process. For more information, please also refer to the FDA guidance entitled *Guideline for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

最终，所述灭菌方法的运行参数应当基于在传热最慢的位置也达到致死性。应当证明灭菌工艺的无菌保证度为 10^{-6} 或更好。请参考 FDA 指南“申请人用和兽用药品时递交无菌工艺验证的文件的指南”。

The sterilizer validation program should continue to focus on the load areas identified as most difficult to penetrate or heat. The suitability of the sterilizer should be established by qualification, maintenance, change control, and periodic verification of the cycle, including biological challenges. Change control procedures should adequately address issues such as a load configuration change or a modification of a sterilizer.

灭菌验证程序应当始终集中在最难穿透或加热的装载区域。应当通过确认、维护、变更控制和对循环的定期检查，包括生物实验性试验，建立灭菌器的适用性。变更控制程序应当充分处理装载类型改变或灭菌器改造等问题。

2. Equipment Controls and Instrument Calibration
设备控制和仪器校准

For both validation and routine process control, the reliability of the data generated by sterilization cycle monitoring devices should be considered to be of the utmost importance. Devices that measure cycle parameters should be routinely calibrated. Written procedures should be established to ensure that these devices are maintained in a calibrated state. For example, we recommend that procedures address the following:

对于验证和日常工艺控制，应当特别注意由灭菌循环监控装置所产生的数据的可靠性。测量循环参数的装置应当定期校准。应建立书面程序，保证这些装置保持在校准状态。比如，我们建议采取下列程序。

- Temperature and pressure monitoring devices for heat sterilization should be calibrated at suitable intervals. The sensing devices used for validation studies should be calibrated before and after validation runs.

  高温灭菌的温度和压力监控装置应当定期校准。验证研究的传感装置应当在验证之前和之后校准。

- Devices used to monitor dwell time in the sterilizer should be periodically calibrated.

  用于监测灭菌器内保压时间的装置应当定期校准。

- The microbial count of a biological indicator should be confirmed. Biological indicators should be stored under appropriate conditions.

  应当确认生物指示器的微生物计数。生物指示器应当在适当的条件下储存。

- If the reliability of a vendor's Certificate of Analysis is established through an appropriate qualification program, the D-value of a biological indicator (e.g., spore strips, glass ampuls) can be accepted in lieu of confirmatory testing of each lot. However, a determination of resistance (D-value) should be performed for any biological indicator inoculated onto a substrate, or used in a way that is other than described by the vendor. D-value determinations can be conducted by an independent laboratory.

  如果通过合适确认程序建立供应商分析报告的可靠性，那么生物指示剂的 D 值可以代替每一批的确认试验。然而，如果将任何生物指示剂接种到基质上，或者使用方法与供应商所述不同，那么应当测定抗性(D 值)。D 值确定可以由独立实验室进行。

- Where applicable, instruments used to determine the purity of steam should be calibrated.

  可能的情况下，校准用于测定蒸汽纯度的仪器。

- For dry heat depyrogenation tunnels, devices (e.g. sensors and transmitters) used to measure belt speed should be routinely calibrated. Bacterial endotoxin challenges should be appropriately prepared and measured by the laboratory.

  在干热除热原隧道，应当定期测定用于测量皮带速度的装置(如：传感器和发送器)。实验室应当合适地准备和测量细菌内毒素试验。

To ensure robust process control, equipment should be properly designed with attention to features such as accessibility to sterilant, piping slope, and proper condensate removal (as applicable). Equipment control should be ensured through placement of measuring devices at those control points that are most likely to rapidly detect unexpected process variability. Where manual manipulations of valves are required for sterilizer or SIP operations, these steps should be documented in manufacturing procedures and batch records. Sterilizing equipment should be properly maintained to allow for consistent, satisfactory function. Routine evaluation of sterilizer performance-indicating attributes, such as equilibrium (come up) time is important in assuring that the unit continues to operate as per the validated conditions.

为了保证严格的工艺控制，设备应有合理设计，使其容易接触灭菌媒介、管线有坡度并且能合适地去除冷凝水(如果合适)。通过在那些最有可能快速检出非预期工艺可变性的控制点放置测量装置，保证设备控制。灭菌器或SIP的操作如果需要人工操作阀门，那么这些步骤应当记录在生产程序和批记录上。应当正确维护灭菌设备，使其一致并且满意地发挥功能。对于指示灭菌器性能的性质，例如平衡时间，进行常规评估，对于保证所述单位持续按照已验证条件发挥功能是重要的。

X. LABORATORY CONTROLS
实验室控制

21 CFR 211.22(b) states that "Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit."

CFR 211.22(b)规定，"QC 应有足够的实验室设施用于测试和批准（或拒绝）药物成分、药品容器、密封、保证材料、过程中材料和药品。"

21 CFR 211.22(c) states that "The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product."

CFR 211.22(c) 规定，"QC 应当有责任批准或拒绝对药品的成分、浓度、质量和纯度有影响的所有程序或规格。"

21 CFR 211.42(c) states, in part, that "Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures: * * * (10) Aseptic processing, which includes as appropriate: * * * (iv) A system for monitoring environmental conditions; * * *."

CFR 211.42(c) 部分规定，"应当在有充足空间的指定区域内进行操作。在某些工艺过程中，企业的操作应有必要的独立或指定区域或类似控制系统以防止污染或混淆，所述工艺工程包括：…(10)无菌加工，所述控制系统包括：…(iv)监测环境质量的系统；…"

21 CFR 211.56(b) states that "There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed."

CFR 211.56(b) 规定，"应当有书面程序，规定卫生责任，并充分描述清洁建筑和厂房时使用的清洁计划、方法、设备和材料；应当遵循所述程序。"

21 CFR 211.56(c) states, in part, that "There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed * * *."

CFR 211.56(c) 部分规定，"应当有书面程序，规定合适灭鼠剂、杀虫剂、杀真菌剂、熏蒸剂和清洁及卫生剂的使用。所述书面程序的设计应能够预防设备、成分、药品容器、密封、包装材料、标签或药品的污染，并且应当遵从…。"

21 CFR 211.110(a) states, in part, that "To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product * * *."

CFR 211.110(a)部分规定，"为保证批次的一致性和药物的完整性，应当建立和遵从书面程序，描述对每一批过程中材料的合适样品应该进行的过程中控制和测试或检查。应当建立所述控制程序，对于可能引起过程中材料和药品特性上可变性的生产工艺，监测其效果并验证其性能…。"

21 CFR 211.113(b) states that "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."

CFR 211.113 (b)规定，"应当建立和遵从设计用于防止无菌药品受到微生物污染的合适书面程序。所述程序应当包括任何灭菌过程的验证。"

21 CFR 211.160(b) states that "Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include: (1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration. (2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified. (3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified. (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used."

CFR 211.160 (b)规定，"实验室控制应当包括建立科学合理的规格、标准、取样计划和测试程序，所述文件在设计上应能够保证药物成分、药品容器、密封、过程中材料、标签和药品符合合适的成分、浓度、质量和纯度标准。实验室控制应当包括：(1)决定每次运来的用于药品生产、工艺、包装或贮存的每一批次药物成分、药品容器、密封和标签与既定书面规格的符合性。所述规格应当包括所使用的取样和测试程序。样品应当有代表性，并且得到充分鉴定。所述程序还应该要求对于可能发生变质的任何药物成分、药品容器或密封的再检。(2)决定过程中材料与书面规格的符合性，并描述其取样和测试程序。所述样品应该有代表性，并且得到适当鉴定。(3)决定药品与书面取样程序以及合适规格的符合性。所述样品应当具有代表性，并且得到适当鉴定。(4)按照既定书面程序，以合适间隔校准仪器、器械、量表和记录仪，所述书面程序包括具体指导、计划、准确度和精密度的限度，并且规定在未达到准确度和/或精密度限度的情况下，应该采取纠正措施。不应当使用未达到成文规格的仪器、器械、量表和记录仪。"

21 CFR 211.165(e) states that "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with § 211.194(a)(2)."

CFR 211.165(e)规定，"企业应当建立和记录所使用试验方法的准确度、灵敏度、特异性和重复性。所述验证和文件化工作应该按照 211.194(a)(2)来完成。"

21 CFR 211.192 states, in part, that "All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed * * *."

CFR 211.192 部分规定，"在某一批次产品放行或分销前，QC 应当审核和批准所有药物生产和控制记录，包括包装和贴签记录，以决定与所有已建立并批准的程序的符合性…。"

A. Environmental Monitoring
环境监测

1. General Written Program
书面程序

In aseptic processing, one of the most important laboratory controls is the environmental monitoring program. This program provides meaningful information on the quality of the aseptic processing environment (e.g., when a given batch is being manufactured) as well as environmental trends of ancillary clean areas. Environmental monitoring should promptly identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs (211.42 and 211.113).

在无菌加工过程中，实验室控制最重要的项目之一是环境监控程序。该程序提供无菌加工环境(如当生产给定批号时)的有意义信息，以及辅助洁净区域环境趋势。环境监测应当及时地发现污染的潜在途径，以允许在产品出现污染前实施纠正措施(211.42 和 211.113)。

Evaluating the quality of air and surfaces in the cleanroom environment should start with a well-defined written program and scientifically sound methods. The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures. Written procedures should include a list of locations to be sampled. Sample timing, frequency, and location should be carefully selected based upon their relationship to the operation performed. Samples should be taken throughout the classified areas of the aseptic processing facility (e.g., aseptic corridors, gowning rooms) using scientifically sound sampling procedures. Sample sizes should be sufficient to optimize detection of environmental contaminants at levels that might be expected in a given clean area.

应当按照良好定义的书面程序和科学合理的方法评估洁净室环境内空气和表面的质量。监测程序应当包括所有生产班次，并且包括空气、地板、墙面和设备表面，包括与产品、容器和密封直接接触的关键表面。书面程序应当包括取样点列表。取样时间、频率和位点应当根据它们与所进行操作的关系而仔细选择。应当使用科学合理的取样程序，从无菌加工设施的所有洁净区域(如无菌走廊、更衣室)取样。样品大小应足以以最佳方式检出给定洁净区域中预期水平的环境污染。

It is important that locations posing the most microbiological risk to the product be a key part of the program. It is especially important to monitor the microbiological quality of the critical area to determine whether or not aseptic conditions are maintained during filling and closing activities. Air and surface samples should be taken at the locations where significant activity or product exposure occurs during production. Critical surfaces that come in contact with the sterile product should remain sterile throughout an operation. When identifying critical sites to be sampled, consideration should be given to the points of contamination risk in a process, including factors such as difficulty of setup, length of processing time, and impact of interventions. Critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing. Detection of microbial contamination on a critical site would not necessarily result in batch rejection. The

contaminated critical site sample should prompt an investigation of operational information and data that includes an awareness of the potential for a low incidence of false positives.

对产品构成最大微生物污染风险的位点是该程序的关键部分。尤其重要的是监测关键区域的微生物质量，以决定分装和封口活动过程中无菌条件是否得到维持。在生产过程中有重要活动或出现产品暴露的位点，应当取空气和表面样品。在操作过程中，与无菌产品接触的关键表面应保持无菌。在鉴定需要取样的关键位点时，应当考虑工艺中存在污染风险的位点，并且考虑其它因素，例如设置的困难、工艺时间程度和干预的影响。关键表面的取样应当在无菌工艺操作结束时进行，以避免工艺过程中与无菌表面的直接接触。在关键位点检测到微生物污染不一定导致拒绝该批。在关键位点样品发现污染后，应当对操作信息和数据进行调查，包括出现可能性比较低的假阳性。

Environmental monitoring methods do not always recover microorganisms present in the sampled area. In particular, low-level contamination can be particularly difficult to detect. Because false negatives can occur, consecutive growth results are only one type of adverse trend. Increased incidence of contamination over a given period is an equal or more significant trend to be tracked. In the absence of any adverse trend, a single result above an action level should trigger an evaluation and a determination about whether remedial measures may be appropriate. In all room classes, remedial measures should be taken in response to unfavorable trends.

环境检测方法不一定总能回收取样区域内存在的微生物。具体地说，低水平污染特别难以检出。因为可能出现假阳性，所以连续出现生长的结果仅是不良趋势的一种类型。给定时间内污染出现率增加是一种需要追踪的同样重要或者更重要的趋势。在不存在任何不良趋势的情况下，对于在行动限以上的单次阳性结果，应当进行评估，并决定是否需要采取纠正措施。在所有房间级别中，应当根据不良趋势采取纠正措施。

All environmental monitoring locations should be described in SOPs with sufficient detail to allow for reproducible sampling of a given location surveyed. Written SOPs should also address elements such as (1) frequency of sampling, (2) when the samples are taken (i.e., during or at the conclusion of operations), (3) duration of sampling, (4) sample size (e.g., surface area, air volume), (5) specific sampling equipment and techniques, (6) alert and action levels, and (7) appropriate response to deviations from alert or action levels.

在 SOP 中应当详细描述所有环境监测位点，以便对给定位点取样的可重复性。书面 SOP 应当说明下列因素：(1)取样频率，(2)取样时间(如： 在操作结束时)，(3)取样的持续时间，(4)样品大小(如：表面区域、空气容量)，(5)具体取样设备和技术，(6)警戒限和行动限，以及(7)超过警戒限或行动限情况时的合适应对措施。

2. Establishing Levels and a Trending Program
建立限度和趋势分析程序

Microbiological monitoring levels should be established based on the relationship of the sampled location to the operation. The levels should be based on the need to maintain adequate microbiological control throughout the entire sterile manufacturing facility. One should also consider environmental monitoring data from historical databases, media fills, cleanroom

qualification, and sanitization studies, in developing monitoring levels. Data from similar operations can also be helpful in setting action and alert levels, especially for a new operation.

微生物监测限度应当基于取样地点与操作的关系。各个限度应当基于充分维持对整个无菌生产设施的微生物控制的需要。在建立监测限度时，也应当考虑来自历史数据库、培养基罐装试验、洁净房确认以及消毒研究中得到的环境监测数据。相似操作过程得到的数据也有助于设定行动限和警戒限，对于新的操作尤其如此。

Environmental monitoring data will provide information on the quality of the manufacturing environment. Each individual sample result should be evaluated for its significance by comparison to the alert or action levels. Averaging of results can mask unacceptable localized conditions. A result at the alert level urges attention to the approaching action conditions. A result at the action level should prompt a more thorough investigation. Written procedures should be established, detailing data review frequency and actions to be taken. The quality control unit should provide routine oversight of near-term (e.g., daily, weekly, monthly, quarterly) and long-term trends in environmental and personnel monitoring data.

环境监测数据将提供生产环境质量方面的信息。根据与警戒限或行动限的比较，评估每个样品测试结果的显著性。结论的平均数可能掩盖不合格的局部环境。达到警戒限的结果促请关注接近行动限的条件。对于达到行动限的结果应当开展更彻底的调查。应当建立书面程序，详细规定数据回顾频率以及要采取的行动。QC 部门应当对环境监测和人员监控数据的近期（如：每天、每周、每月、每季）和长期趋势进行日常检查。

Trend reports should include data generated by location, shift, room, operator, or other parameters. The quality control unit should be responsible for producing specialized data reports (e.g., a search on a particular isolate over a year period) with the goal of investigating results beyond established levels and identifying any appropriate follow-up actions. Significant changes in microbial flora should be considered in the review of the ongoing environmental monitoring data.

趋势分析报告应当包括根据地点、班次、房间、操作员或其它参数产生的数据。QC 部门应当负责编制专门的数据报告(如在一年期内某种分离物的搜索)，目的是调查超出既定水平的结果并说明任何合适的追踪行动。回顾持续的环境监测数据时，应当考虑微生物群落的显著变化。

Written procedures should define the system whereby the most responsible managers are regularly informed and updated on trends and investigations.

书面程序应当确定一个系统，能够定期及时通知直接负责经理关于趋势和调查的信息。

3. Disinfection Efficacy
消毒功效

The suitability, efficacy, and limitations of disinfecting agents and procedures should be assessed. The effectiveness of these disinfectants and procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces.

应当评估消毒剂和消毒程序的适用性、功效和限制性。这些消毒剂和消毒程序有效性的评价标准是它们保证从表面充分去除潜在污染物的能力。

To prevent introduction of contamination, disinfectants should be sterile, appropriately handled in suitable (e.g., sterile) containers and used for no longer than the predefined period specified by written procedures. Routinely used disinfectants should be effective against the normal microbial vegetative flora recovered from the facility. Many common disinfectants are ineffective against spores. For example, 70 percent isopropyl alcohol is ineffective against *Bacillus* spp. spores. Therefore, a sound disinfectant program also includes a sporicidal agent, used according to a written schedule and when environmental data suggest the presence of sporeforming organisms.

为了防止引入感染，消毒剂应当是无菌的，在合适的(如无菌)密封容器中处理，而且时间不超过书面程序所规定的期限。日常使用的消毒剂应当有效针对从厂房设施回收的有活力的常见微生物群落。许多常见的消毒剂对孢子是无效的。比如：70%的异丙醇对芽孢杆菌孢子无效。因此，合理的杀菌程序也包括一个杀孢子剂，根据书面计划和当环境数据指出有形成孢子的微生物存在时使用。

Disinfection procedures should be described in sufficient detail (e.g., preparation, work sequence, contact time) to enable reproducibility. Once the procedures are established, their adequacy should be evaluated using a routine environmental monitoring program. If indicated, microorganisms associated with adverse trends can be investigated as to their sensitivity to the disinfectants employed in the cleanroom in which the organisms were isolated.

消毒程序应当充分详细描述(如：准备、工作顺序、接触时间)，以保证重复性。一旦建立程序，应当通过日常环境监测程序来衡量它们的充分性。如果有指示，可以调查从洁净室中分离的与不利趋势相关的微生物对于在所述洁净室中使用的消毒剂的敏感性。

4. Monitoring Methods
监测方法

Acceptable methods for monitoring the microbiological quality of the environment include:

可行的环境微生物质量监测方法包括：

a. Surface Monitoring
表面监测

Environmental monitoring involves sampling various surfaces for microbiological quality. For example, product contact surfaces, floors, walls, and equipment should be tested on a regular basis. Touch plates, swabs, and contact plates can be used for such tests.

环境监控包括在不同表面取样以评估微生物质量。例如，应当定期检测产品接触表面、地面、墙和设备。接触平板和棉签可用于此类检测。

b. Active Air Monitoring
主动空气监测

Assessing microbial quality of air should involve the use of *active* devices including but not limited to impaction, centrifugal, and membrane (or gelatin) samplers. Each device has certain advantages and disadvantages, although all allow testing of the number of organisms per volume of air sampled. We recommend that such devices be used during each production shift to evaluate aseptic processing areas at carefully chosen locations. Manufacturers should be aware of a device's air monitoring capabilities, and the air sampler should be evaluated for its suitability for use in an aseptic environment based on collection efficiency, cleanability, ability to be sterilized, and disruption of unidirectional airflow.[20] Because devices vary, the user should assess the overall suitability of a monitoring device before it is placed into service. Manufacturers should ensure that such devices are calibrated and used according to appropriate procedures.

衡量空气的微生物质量应当包括使用主动取样装置，包括但不限于冲击、离心和膜(或凝胶)取样器。每一个装置都有一些优点和缺点， 虽然每一种装置都允许测试单位体积取样空气内微生物的数量。我们建议在每个生产班次期间使用这些装置，在仔细选择的位置评估无菌加工区域。药品生产者应当了解装置的空气监测能力，根据收集效率、可清洁性、可灭菌性和对层流的破坏，评估空气采样器在无菌环境中的适用性。[20]由于装置的不同，使用者应当在使用监控装置前，衡量它的整体适用性。药品生产者应当确保这些装置根据合适程序校准和使用。

c. Passive Air Monitoring (Settling Plates)
被动空气监测(沉降菌)

Another method is the use of passive air samplers, such as settling plates (petri dishes containing nutrient growth medium exposed to the environment). Because only microorganisms that settle onto the agar surface are detected, settling plates can be used as qualitative, or semi-quantitative, air monitors. Their value in critical areas will be enhanced by ensuring that plates are positioned in locations posing the greatest risk of product contamination. As part of methods validation, the quality control laboratory should evaluate what media exposure conditions optimize recovery of low levels of environmental isolates. Exposure conditions should preclude desiccation (e.g., caused by lengthy sampling periods and/or high airflows), which inhibits recovery of microorganisms. The data generated by passive air sampling can be useful when considered in combination with results from other types of air samples.

[20] For example, the volume of air sampled should be sufficient to yield meaningful measurements of air quality in a given environment.

[20] 如： 空气取样量应当足以产生给定环境内空气质量有意义的测量结果。

另一个方法是使用被动空气采样器，比如沉降菌（装着暴露在环境下的盛有营养培养基的培养皿）。因为只能检测落到琼脂表面的微生物，沉降菌可以用于定性或半定量的空气监测。将平板放在产品最有可能受到污染的位置，增强该方法监测关键区域的能力。作为试验方法验证的一部分，QC 实验室应当衡量哪一种培养基暴露条件可以优化回收低水平环境分离物。暴露条件应当防止干燥（如：由于取样时间太长和/或快速空气流动），因为这可以抑制微生物的回收。当与通过其它空气采样类型获得的数据结合起来考虑时，被动空气取样产生的数据可能是有用的。

B. Microbiological Media and Identification
微生物培养基和微生物鉴定

Characterization of recovered microorganisms provides vital information for the environmental monitoring program. Environmental isolates often correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for an investigation. Monitoring critical and immediately surrounding clean areas as well as personnel should include routine identification of microorganisms to the species (or, where appropriate, genus) level. In some cases, environmental trending data have revealed migration of microorganisms into the aseptic processing room from either uncontrolled or lesser controlled areas. Establishing an adequate program for differentiating microorganisms in the lesser-controlled environments, such as Class 100,000 (ISO 8), can often be instrumental in detecting such trends. At minimum, the program should require species (or, where appropriate, genus) identification of microorganisms in these ancillary environments at frequent intervals to establish a valid, current database of contaminants present in the facility during processing (and to demonstrate that cleaning and sanitization procedures continue to be effective).

对回收微生物的表征为环境监测程序提供关键信息。环境分离物通常与在培养基罐装试验或产品无菌测试失败中发现的污染物相关，而总体环境情况为调查提供有用信息。对关键区域及其临近洁净区域以及人员的监测应当包括鉴定微生物达到物种水平(合适的情况下，达到属水平)。在一些情况下，环境趋势数据揭示微生物从非控制区或较低级别区域到无菌操作间的迁移。建立充分程序，区分较低级别环境如 100,000 级(ISO 8)中的微生物，通常有助于检出这种趋势。至少程序应当要求定期对这些辅助环境中的微生物进行物种鉴定(或者在合适情况下，属鉴定)，建立工艺过程中厂房内存在的污染物的当前数据库(以及证明清洁和消毒程序持续有效)。

Genotypic methods have been shown to be more accurate and precise than traditional biochemical and phenotypic techniques. These methods are especially valuable for investigations into failures (e.g., sterility test; media fill contamination). However, appropriate biochemical and phenotypic methods can be used for the routine identification of isolates.

已被证明，基因型方法比传统的生物化学和表型方法更为准确和精确。这些方法对失败调查特别有价值（如： 无菌测试，培养基罐装试验污染）。然而，适当的生物化学和表型方法可以用于分离物的常规鉴定。

The goal of microbiological monitoring is to reproducibly detect microorganisms for purposes of monitoring the state of environmental control. Consistent methods will yield a database that allows for sound data comparisons and interpretations. The microbiological culture media used in environmental monitoring should be validated as capable of detecting fungi (i.e., yeasts and molds) as well as bacteria and incubated at appropriate conditions of time and temperature. Total aerobic bacterial count can be obtained by incubating at 30 to 35°C for 48 to 72 hours. Total combined yeast and mold count can generally be obtained by incubating at 20 to 25°C for 5 to 7 days.

微生物监控的目的是可重复地检测微生物，以监测环境控制状况。 一致的方法可以产生允许合理数据比较和解释的数据库。环境监测中使用的微生物培养基应当经过验证，能够检出真菌（如：酵母和霉菌）和细菌，在适当时间和温度条件下能够培养。在 30 到 35°C 温度下培养 48 到 72 小时后，获得总好氧细菌计数。通常在 20-25°C 培育 5-7 天后，获得酵母和霉菌的总数目。

Incoming lots of environmental monitoring media should be tested for their ability to reliably recover microorganisms. Growth promotion testing should be performed on all lots of prepared media. Where appropriate, inactivating agents should be used to prevent inhibition of growth by cleanroom disinfectants or product residuals (e.g., antibiotics).

应当测试所有批次已准备的环境监测培养基可靠回收微生物。在所有准备的培养基上应当进行生长促进试验。合适的情况下，应当使用灭活剂预防洁净室消毒剂或产品残余物(如抗生素)抑制微生物生长。

C. Prefiltration Bioburden
过滤前生物负荷

Manufacturing process controls should be designed to minimize the bioburden in the unfiltered product. In addition to increasing the challenge to the sterilizing filter, bioburden can contribute impurities (e.g., endotoxin) to, and lead to degradation of, the drug product. A prefiltration bioburden limit should be established.

生产工艺控制应当设计成为最小化未过滤产品中的生物负荷。生物负荷除增加对除菌滤器的挑战外，还增加药品中的杂质(如内毒素)，并导致药品降解。应当建立过滤前生物负荷限度。

D. Alternate Microbiological Test Methods
可替代的微生物检测方法

Other suitable microbiological test methods (e.g., rapid test methods) can be considered for environmental monitoring, in-process control testing, and finished product release testing after it is demonstrated that the methods are equivalent or better than traditional methods (e.g.,USP).

另外的一些合适的微生物测试方法（如：快速测试法），在证明与传统方法（如： 美国药典）等价或更好后，可以考虑用于环境监控、工艺中控制测试及成品放行测试 。

E. Particle Monitoring
颗粒监测

Routine particle monitoring is useful in rapidly detecting significant deviations in air cleanliness from qualified processing norms (e.g., clean area classification). A result outside the established classification level at a given location should be investigated as to its cause. The extent of investigation should be consistent with the severity of the *excursion* and include an evaluation of trending data. Appropriate corrective action should be implemented, as necessary, to prevent future deviations.

常规微粒监控可用于快速检出空气洁净度从合格工艺标准(如洁净区域分级)的显著偏离。如果给定位置的监测结果超出规定的分级标准，应当调查原因。调查的程度应当与偏差的严重性相一致，包括对趋势数据的评估。必要时应当采取合适的纠正措施，防止以后的偏差。

See Section IV.A for additional guidance on particle monitoring.

关于微粒控制的其它指南请参照第 9 章 A 部分。

XI. STERILITY TESTING / 无菌试验

21 CFR 210.3(b)(21) states that "*Representative sample* means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled."

21CFR210.3(b)(21)规定，"代表性样品指由一定量单位组成的样品，根据合理标准如随机取样获得，并确保所述样品准确描述被取样的材料。"

21 CFR 211.110(a) states, in part, that "To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."

21CFR211.110(a)部分规定，"为了确保药品批的一致性和完整性，需建立及遵从描述在每批工艺中材料的合适样品进行的工艺中控制和测试或检查的书面程序。应当建立这些控制程序，以监控产品，并验证那些可能引起工艺中材料和药品特性的可变性的生产工艺的性能。"

21 CFR 211.160(b) states that "Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include: (1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration. (2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified. (3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified. (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used."

21CFR211.160(b)规定，"实验室控制应当包括建立科学、合理和合适的规格、标准、取样计划、测试程序，以保证药品成分、药品容器、密封、生产中材料、标签及药品符合成分、浓度、质量及纯度的恰当标准。实验室控制应当包括：(1)确定用于药品生产、加工、包装或贮存的每次进货中每一批药品成分、药品容器、密封和标签与合适书面规格的符合性。规格应当包括对所使用取样和测试程序的描述。样品应当具有代表性并得到充分鉴定。这些程序也应当要求对可能变质的药品成分、药品容器和密封的合适的再检。(2)确定工艺中材料与书面规格的符合性，并描述其取样和测试程序。这些样品应当具有代表性而且经过合适鉴定。(3)确定与取样程序书面描述和药品合适规格的符合性。这些样品应当具有代表性并且经过合适鉴定。(4)按照成文程序以合适间隔对仪表、仪器、测量仪器和记录装置进行校准，所述程序包括准确度和精确度的具体指导、计划和限度，并规定在未达到准确度和/或精确度限度的情况下采取补救措施。不应当使用没有达到规定规格的仪表、仪器、测量仪器和记录装置。"

21 CFR 211.165(a) states, in part, that "For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release * * *."

21CFR211.165(a)部分规定，"对于每批药品，放行前应有合适的实验室确认，保证其与药品成品规格的完全符合性…。"

21 CFR 211.165(e) states that "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with §

211.194(a)(2)."

21CFR211.165(e)规定，"企业应当建立和记录所使用试验方法的准确性、灵敏性、特异性及重复性。这些验证和文件化可根据 211.194.(a)(2)来完成。"

21 CFR 211.167(a) states that "For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed."

21CFR211.167(a)规定，"对于每批无菌和/或无热原药品，应当有恰当的实验室测试证实其与所述要求的符合性。测试程序应形成文件并得到遵从。"

21 CFR 211.180(e) states, in part, that "Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures * * *."

21CFR211.180(e)部分规定，"此章要求的书面记录应当保存，以便数据可以用于至少每年一次对每种药品质量标准的评估，以确定药品规格或生产或控制程序变更的需要…。"

21 CFR 211.192 states that "All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup."

21CFR211.192 规定，"在放行或分销某批产品前，QC 部门应当审核和批准所有药品生产和控制记录，包括包装和贴签记录，以确定其与所有已经建立并批准的书面程序的符合性。无论一批产品是否已经分销，该批产品的任何无法解释的差异(包括理论产量超出主生产文件和主控制文件中建立的最大或最小百分率)或失败以及任何成分与规格中任一项的符合性都应当得到充分调查。调查应当延伸到同一药品的其它批次，或与具体失败或差异相关的其它药品。调查应形成书面记录，并应包括结论和追踪。"

Certain aspects of sterility testing are of particular importance, including control of the testing environment, understanding the test limitations, and investigating manufacturing systems following a positive test.

无菌测试的一些方面特别重要，包括测试环境控制、对测试局限性的了解、以及在出现阳性结果后调查生产系统。

The testing laboratory environment should employ facilities and controls comparable to those used for aseptic filling operations. Poor or deficient sterility test facilities or controls can result in test failure. If production facilities and controls are significantly better than those for sterility testing, the danger exists of mistakenly attributing a positive sterility test result to a faulty laboratory even when the product tested could have, in fact, been nonsterile. Therefore, a manufacturing deficiency may go undetected. The use of isolators for sterility testing minimizes the chance of a false positive test result.

测试实验室环境应当使用与无菌分装操作等同的设施和控制。劣质或有缺陷的无菌测试设施或控制可能导致测试失败。如果生产设施和控制比用于无菌测试的设施和控制显著更好，那么有可能在产品实际上已经受到污染的情况下，错误地把阳性无菌测试结果归咎于实验室的不足。因此，生产的缺陷可能会被漏检。无菌测试时使用隔离装置减少了假阳性测试结果的可能性。

A. Microbiological Laboratory Controls
微生物实验室控制

Sterility testing methods are required to be accurate and reproducible, in accordance with 211.194 and 211.165. USP <71> *"Sterility Tests"* is the principal source used for sterility testing methods, including information on test procedures and media.[21]

根据 211.194 和 211.165，无菌测试方法应当准确并且可重复。美国药典<71>“无菌测试”是无菌测试方法的主要来源，包括测试程序和培养基的信息。[21]

As a part of methods validation, appropriate microbiological challenge testing will demonstrate reproducibility of the method to reliably recover representative microorganisms. If growth is inhibited, modifications (e.g., increased dilution, additional membrane filter washes, addition of inactivating agents) to the test method should be implemented to optimize recovery. Ultimately, methods validation studies should demonstrate that the method does not provide an opportunity for false negatives.

作为方法验证的一部分，适当的微生物挑战试验可以证明方法可靠回收代表性微生物的可重复性。如果生长受到抑制，应当改变测试方法来优化回收（如： 增加稀释度，增加膜滤器清洗，增加灭活剂）。方法验证研究最终应当证明该方法不会导致假阴性。

It is essential that the media used to perform sterility testing be rendered sterile and demonstrated as growth promoting. Personnel performing sterility testing should be qualified and trained for the task. A written program should be in place to maintain updated training of personnel and confirm acceptable sterility testing practices.

用于操作无菌测试的培养基应当是无菌的，并证明能够促进生长。 操作无菌测试的人员应当胜任工作并受过训练。应当有一个书面程序来 记录人员的培训资料，确认合格的无菌测试实践。

B. Sampling and Incubation
取样和培育

Sterility tests are limited in their ability to detect contamination because of the small sample size typically used. For example, as described by USP, statistical evaluations indicate that the sterility test sampling plan "only enables the detection of contamination in a lot in which 10% of the units are contaminated about nine times out of ten in making the test" (Ref. 13). To further

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illustrate, if a 10,000-unit lot with a 0.1 percent contamination level was sterility tested using 20 units, there is a 98 percent chance that the batch would pass the test.

由于通常使用的样品较小，无菌测试发现感染的能力有限。比如： 根据美国药典，统计评估表明，无菌测试取样计划“在 10%单位受到污染的批次中，10 次检测只有 9 次能够检出污染”（参考文献 13)。更一步说，如果一个 10,000 单位的批存在 0.1%的污染水平，无菌测试使用 20 个单位，那么 98%的机会这批产品会通过无菌测试。

It is important that the samples represent the entire batch and processing conditions. Samples should be taken:

样品应当能代表整个批及加工环境，取样应当：

- at the beginning, middle, and end of the aseptic processing operation

  在无菌加工操作的开始、中间和结束时进行。

- in conjunction with processing interventions or excursions

  与加工干预和误差相结合。

Because of the limited sensitivity of the test, any positive result is considered a serious CGMP issue that should be thoroughly investigated.

由于测试灵敏度有限，任何阳性结果都应当被认为是一个不符合 cGMP 的重要事件，需要彻底调查。

C. Investigation of Sterility Positives
无菌试验阳性的调查

Care should be taken in the performance of the sterility test to preclude any activity that allows for possible sample contamination. When microbial growth is observed, the lot should be considered nonsterile and an investigation conducted. An initial positive test would be invalid only in an instance in which microbial growth can be unequivocally ascribed to laboratory error.

在进行无菌测试操作时应当采取措施，预防任何可能造成样品感染的活动。当观察到微生物生长时，应当认为该批受到污染，并进行调查。只有在微生物生长能够毫无疑义地归因于实验室失误的情况下，才能否定最初的阳性测试结果。

Only if conclusive and documented evidence clearly shows that the contamination occurred as part of testing should a new test be performed. When available evidence is inconclusive, batches should be rejected as not conforming to sterility requirements.

只有在结论性的书面证据清楚显示所述污染是测试引起的情况下，才应当进行新测试。如果得到的证据不是结论性的，那么应当以不符合无菌性要求为由，拒绝该批。

After considering all relevant factors concerning the manufacture of the product and testing of the samples, the comprehensive written investigation should include specific conclusions and identify corrective actions. The investigation's persuasive evidence of the origin of the contamination should be based on at least the following:

在考虑有关样品生产和测试的所有相关因素后，全面的书面调查应当包括具体的结论，并指出补充行动方案。调查过程中，关于感染来源的有说服性证据应当基于至少以下几点：

1. *Identification (speciation) of the organism in the sterility test*
   鉴定在无菌测试中发现的有机体(物种)

Sterility test isolates should be identified to the species level. Microbiological monitoring data should be reviewed to determine if the organism is also found in laboratory and production environments, personnel, or product bioburden. Advanced identification methods (e.g., nucleic-acid based) are valuable for investigational purposes. When comparing results from environmental monitoring and sterility positives, both identifications should be performed using the same methodology.

无菌测试分离物应当鉴定到物种水平。应当回顾微生物监测数据，确定在实验室和生产环境、人员或产品生物负荷中也发现该生物。先进的验证方法（如：以核酸为基础）对调查目的是有效的。当比较从环境检测和无菌测试阳性获得的结果时，两次鉴定都应使用同一方法进行。

2. *Record of laboratory tests and deviations*
   实验室测试和偏差的记录

Review of laboratory deviation and investigation findings can help to eliminate or implicate the laboratory as the source of contamination. For example, if the organism is seldom found in the laboratory environment, product contamination is more likely than laboratory error. If the organism is found in laboratory and production environments, it can still indicate product contamination.

实验室偏差和调查发现的回顾可以有助于排除或发现是否实验室是感染源。如：如果在实验室环境中很少发现该生物，那么产品污染就可能不是实验室错误。如果在实验室和生产环境内发现该生物，那么仍然有可能产品受到感染。

The proper handling of deviations is an essential aspect of laboratory control. When a deviation occurs during sterility testing, it should be documented, investigated, and remedied. If any deviation is considered to have compromised the integrity of the sterility test, the test should be invalidated immediately without incubation.

偏差的恰当处理是实验室控制的一个基本方面。在无菌测试中如果出现偏差，应当记录、调查和补救。如果认为任何偏差已经影响无菌测试的完整性，那么应当立即认为该测试无效，不进行培育。

A sterility positive result can be viewed as indicative of production or laboratory problems, and the entire manufacturing process should be comprehensively investigated since such problems often can extend beyond a single batch. To more accurately monitor potential contamination sources, we recommend keeping separate trends by appropriate categories such as product, container type, filling line, sampling, and testing personnel. Where the degree of sterility test sample manipulation is similar for a terminally sterilized product and an aseptically processed product, a higher rate of initial sterility failures for the latter should be taken as indicative of aseptic processing production problems.

应当认为无菌测试阳性结果指出生产或实验室存在问题，并且应当深入全面地调查整个生产工艺，因为这样的问题的范围常常超出单批药品。为了更准确地监控潜在的感染源，我们建议用合适的分类保持单独的趋势分析，如产品、容器类型、分装线、取样和测试人员。在最终灭菌产品和无菌加工产品的无菌测试样品操作程度相似的情况下，后者无菌测试失败率更高应当认为是无菌加工生产存在问题的标志。

Microbial monitoring of the aseptic area of the laboratory and personnel can also reveal trends that are informative. Upward trends in the microbial load in the aseptic area of the laboratory should be promptly investigated as to cause, and corrected. In some instances, such trends can appear to be more indicative of laboratory error as a possible source of a sterility test failure.

实验室和个人的无菌区域的微生物监测可以显示有意义的趋势。应当及时调查实验室无菌区域的微生物负荷趋势上升的原因，并纠正。在有些情况下，这种趋势可能表明实验室误差是无菌测试失败的原因。

Where a laboratory has a good track record with respect to errors, this history can lower suspicion of the lab as a source of contamination since chances are higher that the contamination arose from production. However, the converse is not true. Specifically, where a laboratory has a poor track record, firms should not assume that the contamination is automatically more attributable to the laboratory and consequently overlook a genuine production problem. Accordingly, it is essential that all sterility positives be thoroughly investigated.

在实验室有关于误差的良好记录的情况下，这个历史可以降低实验室是污染源的怀疑，因为污染更有可能来自生产。但是，反过来并不正确。具体地说，在实验室记录不足的情况下，企业不能假设污染可以自动地归因于实验室，并因此忽视真正的生产问题。因此，有必要彻底调查所有无菌试验阳性结果。

3. *Monitoring of production area environment*
   监测生产区域环境

Trend analysis of microorganisms in the critical and immediately adjacent areas is especially helpful in determining the source of contamination in a sterility failure investigation. Consideration of environmental microbial data should not be limited to results of monitoring the production environment for the lot, day, or shift associated with the suspect lot. For example, results showing little or no recovery of microorganisms can be misleading, especially when preceded or followed by a finding of an adverse trend or atypically high microbial counts. It is therefore important to look at both short- and long-term environmental trend analyses.

在无菌试验失败调查时，对关键区域和临近区域的微生物趋势分析对于确定污染源尤其有帮助。对环境微生物数据的考虑不应只限于与怀疑批有关的当批、当天或当班次的生产环境监测结果。例如，显示回收很少或没有回收微生物的结果可能是误导性的，尤其是在发现不利趋势或不正常的高微生物计数之前或之后。因此，重要的是查看短期和长期的环境趋势分析。

4. *Monitoring Personnel*
   人员监测

The review of data and associated trends from daily monitoring of personnel can provide important information indicating a route of contamination. The adequacy of personnel practices and training also merit significant review and consideration.

对每日人员监控数据和有关趋势的回顾可以提供指示污染途径的重要信息。人员实践和培训的充分性也有利于重要的回顾。

5. *Product Presterilization Bioburden*
   产品灭菌前的生物负荷

We recommend review of trends in product bioburden and consideration of whether adverse bioburden trends have occurred.

我们建议回顾产品生物负荷趋势，考虑是否已经出现不利的生物负荷趋势。

6. *Production record review*
   生产记录审核

Complete batch and production control records should be reviewed to detect any signs of failures or anomalies that could have a bearing on product sterility. For example, the investigation should include elements such as:

应当审核完整的批记录和生产控制记录，发现任何可能影响产品无菌性的失败和异常。如：调查应当包括下列因素：

- Events that could have impacted on the critical zone

  可能影响关键区域的事件

- Batch and trending data that indicate whether utility and/or support systems are functioning properly. For instance, records of air quality monitoring for filling lines could show a time at which there was improper air balance or an unusually high particle count.

显示公用工程和支持系统是否运作正常的批数据和趋势数据。比如：分装线空气质量监测记录可以显示有不恰当的空气平衡或不正常的高颗粒记数的时间。

- Whether construction or maintenance activities could have had an adverse impact

  建造和维护活动是否有不利影响。

7. *Manufacturing history*
   生产历史

The manufacturing history of a product or similar products should be reviewed as part of the investigation. Past deviations, problems, or changes (e.g., process, components, equipment) are among the factors that can provide an indication of the origin of the problem.

作为调查的一部分，应当回顾产品和相似产品的生产历史。过去的偏差、问题或变更(如： 工艺、药品成分、设备)都可以成为指出问题的根源的因素。

XII. BATCH RECORD REVIEW: PROCESS CONTROL DOCUMENTATION
批记录审核：工艺控制文件化

21 CFR 211.100(a) states that "There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit."

21CFR211.100(a) 规定，"应当有生产及加工控制的书面程序，目的是为了保证药品应该具有的成分、浓度、质量和纯度。这些程序应当包括本章内的所有要求。这些书面程序， 包括任何变更，都应当由合适的组织单位起草、审核并通过，并由 QC 部门审核和批准。"

21 CFR 211.100(b) states that "Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified."

21CFR211.100(b)规定，"应当在执行各种生产及工艺控制功能时遵从书面生产及加工控制程序，在操作时形成记录。从书面程序的任何偏差都应当记录并证明是正当的。"

21 CFR 211.186 and 211.188 address, respectively, "Master production and control records" and "Batch production and control records."

21CFR211.186 及 211.188 分别规定"主生产及控制记录"和"批生产及控制记录"。

21 CFR 211.192 states that "All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup."

21CFR211.192 规定，"在放行或分销某批产品前，QC 部门应当审核和批准所有药品生产和控制记录，包括包装和贴签记录，以确定其与所有已经建立并批准的书面程序的符合性。无论一批产品是否已经分销，该批产品的任何无法解释的差异(包括理论产量超出主生产文件和主控制文件中建立的最大或最小百分率)或失败以及任何成分与规格中任一项的符合性都应当得到充分调查。调查应当延伸到同一药品的其它批次，或与具体失败或差异相关的其它药品。调查应形成书面记录，并应包括结论和追踪。"

Manufacturers should build process and environmental control activities into their aseptic processing operation. It is critical that these activities be maintained and strictly implemented on a daily basis. The requirement for review of all batch records and data for conformance with written procedures, operating parameters, and product specifications prior to arriving at the final release decision for an aseptically processed product calls for an overall review of process and system performance for that given cycle of manufacture. All in-process and laboratory control results must be included with the batch record documentation in accordance with section 211.188. Review of environmental and personnel monitoring data, as well as other data relating to acceptability of output from support systems (e.g., HEPA / HVAC, WFI, steam generator) and

proper functioning of equipment (e.g., batch alarms report; integrity of various filters) are considered essential elements of the batch release decision.

工艺和环境控制活动应构成生产者无菌加工操作的一部分。关键的是每日保持及严格执行这些活动。由于在最终放行无菌加工产品前需要审核所有批记录和数据与书面程序、操作参数和产品规格的符合性，需要对生产给定循环的工艺性能和系统性能进行总体审核。按照 211.188，所有工艺中控制结果和实验室控制结果都应当包括在批记录文件中。批放行决定的基本考虑因素包括审核环境监测和人员监测数据、与支持系统(如 HEPA/HVAC、WFI、蒸汽发生器)输出是否合格有关的其它数据以及设备的正常运行(如批报警报告，各种滤器的完整性)。

While interventions and/or stoppages are normally recorded in the batch record, the manner of documenting these occurrences varies. In particular, line stoppages and any unplanned interventions should be sufficiently documented in batch records with the associated time and duration of the event. In addition to lengthened dwell time of sterile product elements in the critical area, an extensive intervention can increase contamination risk. Sterility failures have often been attributed to atypical or extensive interventions that have occurred as a response to an undesirable event during the aseptic process. Written procedures describing the need for line clearances in the event of certain interventions, such as machine adjustments and any repairs, should be established. Such interventions should be documented with more detail than minor events. Interventions that result in substantial activity near exposed product or container closures or that last beyond a reasonable exposure time should, where appropriate, result in a local or full line clearance.

在批记录中通常记录干预和/或中断，但记录各种事件的方式不同。具体地说，生产线停顿和任何计划外的干扰应当在批记录中充分记录，并记录事件时间和长度。除了无菌产品组成部分在关键区域停留时间延长外，影响广泛的干预可能会增加污染风险。无菌测试失败经常被归因于对无菌加工工程中不利事件的反应而采取的不正常或大量干预。应当建立某些干预出现时需要生产线清场的书面程序，例如机器调整和修理。这些干预的记录应该比不重要的事件更详细。在暴露产品和包装密封附近导致大量活动的干预，或超过合理暴露时间的干预，在合理情况下，应当导致局部或全生产线清场。

Any disruption in power supply, however momentary, that could affect product quality is a manufacturing deviation and must be included in batch records (211.100, 211.192).

可能影响产品质量的任何断电，即使是暂时的，也是生产偏差，应当记录在批记录中。（211.100, 211.192)

APPENDIX 1: ASEPTIC PROCESSING ISOLATORS
附录 1：无菌隔离装置

Aseptic processing using isolation systems separates the external cleanroom environment from the aseptic processing line and minimizes its exposure to personnel. A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control, offers tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing. However, users should remain vigilant to potential sources of operational risk. Manufacturers should also be aware of the need to establish new procedures addressing issues unique to isolators.

无菌加工使用的隔离系统将洁净室外部环境与无菌加工线分开，最小化人员对产品的影响。一个设计良好的正压隔离系统，在有足够的维护、监测和控制程序支持的情况下，提供超越传统无菌加工工艺的实际优势，包括在加工期间减少微生物污染机会。然而，使用者还应当警惕操作带来的潜在风险。药品生产商还应当知道建立解决无菌隔离装置独有问题的专门程序的必要性。

A. Maintenance
维护

1. General
概论

Maintenance of isolator systems differs in some significant respects from the traditional, non-isolated aseptic processing operations. Although no isolator forms an absolute seal, very high integrity can be achieved in a well-designed unit. However, a leak in certain components of the system can constitute a significant breach of integrity. The integrity of gloves, half-suits, and seams should receive daily attention and be addressed by a comprehensive preventative maintenance program. Replacement frequencies should be established in written procedures that ensure parts will be changed before they breakdown or degrade. Transfer systems, gaskets, and seals are among the other parts that should be covered by the maintenance program.

在一些重要方面，隔离系统的维护与传统的非隔离无菌加工系统有所不同。虽然没有隔离系统是完全密封的，但在一个良好设计的单元里，可以达到非常高的密封性。然而，系统中某些部件的泄露可能对完整性造成显著破坏。应当每天检查手套、半截袖和接缝的完整性，并且建立全面的预防性维护程序。应当用书面程序来规定更换频率，保证在这些部分开裂或变质前得到更换。传递系统、垫圈和密封也应当包括在维护程序内。

2. Glove Integrity
手套的完整性

A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity. A preventative maintenance program should be established. The choice of durable glove materials, coupled with a well-justified replacement frequency, are key aspects of good manufacturing practice to be addressed. With every use, gloves should be visually evaluated for any macroscopic physical defect. Physical integrity tests should also be

performed routinely. A breach in glove integrity can be of serious consequence. The monitoring and maintenance program should identify and eliminate any glove lacking integrity and minimize the possibility of placing a sterile product at risk.

一个有问题的手套或袖套（护手）构成一条污染的途径，对隔离装置的完整性造成严重破坏。应当建立预防性维护程序。持久耐用的手套材料以及适当的更换频率是遵从 GMP 的关键方面。每次使用前，应当目测检查手套的任何肉眼可见缺陷。还应当常规进行手套的完整性测试。手套完整性被破坏可能造成严重后果。监控和维护程序应当发现、消除任何缺乏完整性的手套，尽量减少对无菌产品造成风险的可能性。

Due to the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, we recommend affording attention to the sanitary quality of the inner surface of the installed glove and to integrating the use of a second pair of thin gloves.

由于微生物可能通过手套上肉眼可见的洞进入手套，而且由于缺乏高灵敏度的手套完整性测试，我们建议要注意隔离罩的手套内表面的卫生质量，并且操作时再戴上一双薄手套。

B. Design
设计

1. Airflow
气流

There are two types of aseptic processing isolators: *open* and *closed.* Closed isolators employ connections with auxiliary equipment for material transfer. Open isolators have openings to the surrounding environment that are carefully engineered to segregate the inner isolator environment from the surrounding room via overpressure.

有两种无菌加工隔离系统： 开放式的和封闭式的。封闭式隔离系统使用与辅助设备的连接来转移材料。开放式隔离系统有通往周围环境的开口，这些开口经过仔细设计，通过正压使内部隔离环境与周围房间隔离开来。

Turbulent flow can be acceptable within closed isolators, which are normally compact in size and do not house processing lines. Other aseptic processing isolators employ unidirectional airflow that sweeps over and away from exposed sterile materials, avoiding any turbulence or stagnant airflow in the area of exposed sterilized materials, product, and container closures. In most sound designs, air showers over the critical area once and then is systematically exhausted from the enclosure. The air handling system should be capable of maintaining the requisite environmental conditions within the isolator.

封闭式隔离系统内的湍流是可以接受的，封闭式隔离系统通常空间较小，没有安装生产线。其它无菌加工隔离系统使用单向气流 ，这些气流吹过暴露的无菌材料， 应避免在暴露无菌材料、产品和容器密封区域的湍流或气流停滞。在更合理的设计中，空气通过关键

区域一次，然后就从密封系统中依次排出。空调系统应当能维持隔离系统内必要的环境质量。

2. Materials of Construction
   建筑材料

As in any aseptic processing design, suitable materials should be chosen based on durability, as well as ease of cleaning and decontamination. For example, rigid wall construction incorporating stainless steel and glass materials is widely used.

正如在任何无菌加工设计中一样，应当根据耐用性以及是否容易清洁和去除污染来选择合适材料。例如，在坚硬的墙结构中广泛使用不锈钢和玻璃材料。

3. Pressure Differential
   压差

Isolators that include an open portal should be designed to ensure complete physical separation from the external environment. A positive air pressure differential adequate to achieve this separation should be employed and supported by qualification studies. Positive air pressure differentials from the isolator to the surrounding environment have largely ranged from approximately 17.5 to 50 Pascals.[22] The appropriate minimum pressure differential established by a firm will depend on the system's design and, when applicable, its exit port. Air balance between the isolator and other direct interfaces (e.g., dry heat tunnel) should also be qualified.

隔离系统包括开放式的隔离系统在物理设计上应当能与外部环境完全隔离。应当使用能足够实现这种隔离的空气正压差，并由验证资料支持。从隔离系统到周围环境的空气正压差可以在大约 17.5 到 50 Pa 之间。[22]公司所规定的恰当最小压差应当取决于系统设计，在合适的情况下还应考虑出口。应当限定隔离系统和其它直接接口(如：干热通道)的空气平衡。

The positive pressure differential should be coupled with an appropriately designed opening to the external environment to prevent potential ingress of surrounding room air by induction. Induction can result from local turbulent flow causing air swirls or pressure waves that might push extraneous particles into the isolator. Local Class 100 (ISO 5) protection at an opening is an example of a design provision that can provide a further barrier to the external environment.

正压差应当配合一个设计合理的到外部环境的开口，这样可以防止周围房间空气在诱导下的可能进入。局部湍流造成空气旋涡或压力波可能导致将外源颗粒推到隔离系统中。在开口处的局部 100 级(ISO 5)是一个设计实例，能够提供对外部环境的更进一步屏障。

4. Clean Area Classifications
   洁净区域分级

[22] 0.07" to 0.20" water gauge

[20]0.7"到 0.20"的水标

The interior of the isolator should meet Class 100 (ISO 5) standards. The classification of the environment surrounding the isolator should be based on the design of its interfaces (e.g., transfer ports), as well as the number of transfers into and out of the isolator. A Class 100,000 (ISO 8) background is commonly used based on consideration of isolator design and manufacturing situations. An aseptic processing isolator should not be located in an unclassified room.

隔离装置的内部应当符合 100 级(ISO 5)标准。隔离装置周围环境的分级应当基于其接口(如：传递口)的设计，以及进出隔离装置的传递次数。 基于隔离系统设计和生产情况的考虑，通常使用 100,000 级(ISO 8)背景。无菌加工隔离装置不应当位于一个无级别的房间。

C. Transfer of Materials/Supplies
材料/供应的传递

The ability to maintain integrity of a decontaminated isolator can be affected impacted by the design of transfer ports. Various adaptations, of differing capabilities, allow for the transfer of supplies into and out of the isolator.

传递口的设计可能影响已消毒隔离系统保持完整性的能力。不同容量的传递口适应不同量的应用物料进出隔离装置。

Multiple material transfers are generally made during the processing of a batch. Frequently, transfers are performed via direct interface with manufacturing equipment. Properly maintained and operated rapid transfer ports (RTPs) are an effective transfer mechanism for aseptic transfer of materials into and out of isolators. Some transfer ports might have significant limitations, including marginal decontaminating capability (e.g., ultraviolet) or a design that has the potential to compromise isolation by allowing ingress of air from the surrounding room. In the latter case, localized HEPA-filtered unidirectional airflow cover in the area of such a port should be implemented. Isolators often include a *mousehole* or other exit port through which product is discharged, opening the isolator to the outside environment. Sufficient overpressure should be supplied and monitored on a continuous basis at this location to ensure that isolation is maintained.

在药品批加工时通常要进行多次物料传递。通常，物料转移是通过与生产设备的直接接口来进行。适当维护和操作的快速传递口(RTP)是无菌传递材料进出隔离系统的有效转移机制。有些传递口可能会有明显限制，包括最低限度的消毒能力(如：紫外线)，或者有影响隔离能力的设计，允许周围房间空气的进入。 对于后者，应当用局部 HEPA 滤器过滤的单向气流保护这个开口区域。隔离系统通常包括卸料的一个小洞或其它出口，使隔离装置与外部环境相通。应当连续提供和监控足够的正压，以确保维持隔离。

D. Decontamination
消毒

1. Surface Exposure
表面暴露

Decontamination procedures should ensure full exposure of all isolator surfaces to the chemical agent. The capability of a decontaminant to penetrate obstructed or covered surfaces is limited. For example, to facilitate contact with the decontaminant, the glove apparatus should be fully extended with glove fingers separated during the decontamination cycle. It is also important to clean the interior of the isolator per appropriate procedures to allow for a robust decontamination process.

消毒程序应当确保所有隔离装置表面全部暴露于化学试剂。消毒剂渗透阻塞的或覆盖表面的能力有限。如：为了便利与消毒剂的接触，手套装置应当全部伸展，并将手套手指分开。重要的是用合适程序清洁隔离装置内部，保证有效的消毒过程。

2. Efficacy
   功效

The decontamination method should render the inner surfaces of the isolator free of viable microorganisms. Multiple available vaporized agents are suitable for achieving decontamination. Process development and validation studies should include a thorough determination of cycle capability. The characteristics of these agents generally preclude the reliable use of statistical methods (e.g., fraction negative) to determine process lethality (Ref. 13). An appropriate, quantified Biological Indicator (BI) challenge should be placed on various materials[23] and in many locations throughout the isolator, including difficult to reach areas. Cycles should be developed with an appropriate margin of extra kill to provide confidence in robustness of the decontamination processes. Normally, a four- to six-log reduction can be justified depending on the application. The specific BI spore titer used and the selection of BI placement sites should be justified. For example, demonstration of a four-log reduction should be sufficient for controlled, very low bioburden materials introduced into a transfer isolator, including wrapped sterile supplies that are briefly exposed to the surrounding cleanroom environment.

消毒方法应当使隔离系统的内部表面没有活的微生物。多种可用的蒸汽灭菌剂适合于消毒。工艺开发和验证研究应当包括对蒸汽循环能力的确认。这些试剂通常要通过统计学方法(如 fraction negative)的应用来确定消毒过程的致死率(参考文献 13)。另一个适当的方法，应当在各种材料上[23]和隔离装置的许多位置，包括难以接近的区域，放置定量的生物指示剂(BI)。消毒过程应当有足够的杀菌能力，保证消毒工艺的有效性。通常根据应用，应当有 4 到 6 个 log 值的降低。应当证明所使用的具体 BI 孢子滴度和 BI 放置位置的选择是合适的。如：对于要引入隔离装置物品的是受控制的、生物负荷很低的材料，4 log 的降低应当足够，包括暂时暴露于周围洁净室环境的包装好的无菌材料。

The uniform distribution of a defined concentration of decontaminating agent should also be evaluated as part of these studies (Ref. 14). Chemical indicators may also be useful as a qualitative tool to show that the decontaminating agent reached a given location.

[23] If the various isolator materials are thoroughly evaluated during cycle development, a firm might consider placing more focus on material texture and porosity during validation of the decontamination process.

[23] 如果在循环发展期间彻底评价不同的隔离装置材料，制药厂在消毒工艺验证过程中可能考虑将重点更多放在材料的质地和孔率上。

作为这些研究的一部分，还应当评估确定消毒剂浓度的均一分布(参考文献 14)。化学指示剂也可用于显示消毒剂达到给定位置的定性工具。

3. Frequency
频率

The design of the interior and content of an isolator should provide for its frequent decontamination. When an isolator is used for multiple days between decontamination cycles, the frequency adopted should be justified. This frequency, established during validation studies, should be reevaluated and increased if production data indicate deterioration of the microbiological quality of the isolator environment.

隔离装置内部及内容附件的设计应当满足其频繁消毒的需要。当隔离装置在消毒循环之间使用多日时，所使用的消毒频率应有正当理由。如果生产数据表明隔离装置环境的微生物质量变差，应当重新评价并增加在以前验证研究中建立的频率。

A breach of isolator integrity should normally lead to a decontamination cycle. Integrity can be affected by power failures, valve failure, inadequate overpressure, holes in gloves and seams, or other leaks. Breaches of integrity should be investigated. If it is determined that the environment may have been compromised, any product potentially impacted by the breach should be rejected.

在隔离装置完整性招到破坏时应当重新进行消毒循环。电力故障、阀门故障、超压不足、在手套和接缝上的漏洞或其它泄露等等可能影响完整性。应当调查对完整性的破坏。如果确定环境已经被破坏，应当拒绝任何受到该破坏影响的产品。

E. Filling Line Sterilization
分装线灭菌

To ensure sterility of product contact surfaces from the start of each operation, the entire path of the sterile processing stream should be sterilized. In addition, aseptic processing equipment or ancillary supplies to be used within the isolator should be chosen based on their ability to withstand steam sterilization (or equivalent method). It is expected that materials that permit heat sterilization (e.g., SIP) will be rendered sterile by such methods. Where decontamination methods are used to render certain product contact surfaces free of viable organisms, a minimum of a six-log reduction should be demonstrated using a suitable biological indicator.

为了保证从每次操作开始时产品接触表面的无菌性，应当灭菌无菌工艺线的整个管线。此外，应当根据承受蒸气灭菌(或相似方法)的能力，选择无菌加工设备或在隔离装置内使用的辅助物料。能允许热消毒(如：SIP)的材料应当是可以用所述方法消毒的。当使用消毒方法去除某些产品接触表面的活的微生物时，使用合适的生物指示剂应当证明至少 6 个 log 的降低。

F. Environmental Monitoring

环境监测

An environmental monitoring program should be established that routinely ensures acceptable microbiological quality of air, surfaces, and gloves (or half-suits) as well as particle levels, within the isolator. Nutrient media should be cleaned off of surfaces following a contact plate sample. Air quality should be monitored periodically during each shift. For example, we recommend monitoring the exit port for particles to detect any unusual results. Media used for environmental monitoring should not be exposed to decontamination cycle residues, as recovery of microorganisms would be inhibited.

应当建立日常环境监测程序，保证隔离装置内空气、表面和手套(或 half-suit)的微生物质量和尘埃粒子水平在合格范围内。接触平板取样后，从表面清洁去除营养培养基。每个班次定期监测空气质量。例如，我们建议监测出口的尘埃粒子，以检出任何不寻常的结果。用于环境监测的培养基不应当暴露于残余的消毒剂中，因为这会阻止微生物生长。

G. Personnel
人员

Although cleanroom apparel considerations are generally reduced in an isolator operation, the contamination risk contributed by manual factors can not be overlooked. Isolation processes generally include periodic or even frequent use of one or more gloves for aseptic manipulations and handling of material transfers into and out of the isolator. One should be aware that locations on gloves, sleeves, or half suits can be among the more difficult to reach places during decontamination, and glove integrity defects might not be promptly detected. Traditional aseptic processing vigilance remains critical, with an understanding that contaminated isolator gloves can lead to product nonsterility. Accordingly, meticulous aseptic technique standards must be observed (211.113), including appropriate use of sterile tools for manipulations.

虽然在隔离装置内操作时洁净室工作服的考虑一般不多，但可能人工操作引起的污染风险不可忽视。隔离装置操作通常包括定期或频繁使用一双或多双手套，进行无菌操作或处理进出隔离装置的物料转移。应当了解，手套、袖子或半身服上的位置可能是最难消毒的位置，并且手套完整性的缺陷可能不能及时发现。 传统的无菌加工注意事项仍然是关键的，同时理解受污染的隔离装置手套可能导致产品无菌性被破坏。因此，必须认真遵守无菌技术标准(211.113)，包括合理应用无菌操作工具。

APPENDIX 2: BLOW-FILL- SEAL TECHNOLOGY
附录 2： 吹-灌-封技术

Blow-fill-seal (BFS) technology is an automated process by which containers are formed, filled, and sealed in a continuous operation. This manufacturing technology includes economies in container closure processing and reduced human intervention and is often used for filling and packaging ophthalmics, respiratory care products, and, less frequently, injectables. This appendix discusses some of the critical control points of this technology. Except where otherwise noted below, the aseptic processing standards discussed elsewhere in this document should apply to blow-fill-seal technology.

吹—灌—封技术（BFS）是容器在连续操作中形成、分装和密封的全自动工艺。该生产技术的容器密封经济、人员干涉减少、通常用于分装和包装眼科药、呼吸用药，有时用于注射剂。本附录讨论该技术的一些关键控制点。除了以下另外提到的以外，在本文件别处讨论的无菌工艺标准应当适用于吹—灌—封技术。

A. Equipment Design and Air Quality
设备设计和空气质量

Most BFS machines operate using the following steps.

- Heat a plastic polymer resin
- Extrude it to form a parison (a tubular form of the hot resin)
- Cut the parison with a high-temperature knife
- Move the parison under the blow-fill needle (mandrel)
- Inflate it to the shape of the mold walls
- Fill the formed container with the liquid product
- Remove the mandrel
- Seal

大部分 BFS 设备使用以下步骤操作：

- 加热塑料聚合物树脂。
- 拉伸形成雏型（热树脂的管状型）。
- 用高温刀子切割雏型。
- 将雏型移到吹—灌针下（心轴）
- 将其吹成模具内部形状
- 灌装液体产品进入已成型的容器
- 移开心轴
- 封口

Throughout this operation, sterile-air is used, for example, to form the parison and inflate it prior to filling. In most operations, the three steps with the greatest potential for exposure to particle contamination and/or surrounding air are those in which (1) the parison is cut, (2) the parison is moved under the blow-fill mandrel, and (3) the mandrel is removed (just prior to sealing).

在该操作过程中，使用无菌空气，例如，形成雏型和在分装前吹成形。在大多数操作中，最有可能暴露于颗粒污染和/或周围环境空气的三个步骤是：（1）切割雏型时，（2）将雏型移至吹-灌心轴时， (3)移开心轴时（封口前）。

BFS machinery and its surrounding barriers should be designed to prevent the potential for extraneous contamination. As with any aseptic processing operation, it is critical that product contact surfaces be sterile. A validated steam-in-place cycle, or equivalent process, should be used to sterilize the equipment path through which the product is conveyed. In addition, any other surface that represents a potential contamination risk to the sterile product should be sterile.

BFS 装置和它的周围障碍物的设计应当防止外来干涉感染的可能。就象任何一个无菌工艺操作，产品接触表面需无菌。应当使用经过验证的在位灭菌循环或等同工艺灭菌传输产品的设备管线。 此外，任何其它可能造成无菌产品的污染风险的表面都应当是无菌的。

The classified environment surrounding BFS machinery should generally meet Class 100,000 (ISO 8), or better, standards, depending on the design of the BFS machinery and the surrounding room. HEPA-filtered or sterile air provided by membrane filters should be used during the steps when sterile products or materials are exposed (e.g., parison formation, container molding or filling steps). Air in the critical area should meet Class 100 (ISO 5) microbiological standards during operations. A well-designed BFS system should also normally achieve Class 100 (ISO 5) airborne particle levels. Only personnel who have been qualified and appropriately gowned should enter the classified environment surrounding the BFS machinery. Refer to Section V of this document for guidance on personnel training, qualification, and monitoring.

在 BFS 装置的周围的有级别环境应当达到万级（ISO 8）或更高标准, 这取决于 BFS 装置和周围房间的设计。 在无菌产品或物料暴露的步骤（如：雏型成型，容器成型或分装步骤），应当使用 HEPA 过滤或由膜过滤器提供的无菌空气。操作期间，在关键区域的空气应当达到 100 级(ISO 5)微生物标准。设计良好的 BFS 系统也应当达到 100 级(ISO 5)空气颗粒标准。只有合格并且适当着装的人员才可进入 BFS 设备周围的有级别环境。参照第 5 章关于人员的培训、确认及监控的内容。

BFS equipment design typically calls for use of specialized measures to reduce particle levels that can contaminate the exposed product. In contrast to nonpharmaceutical applications using BFS machinery, control of air quality (i.e., particles) is critical for sterile drug product manufacture. Particles generated during the plastic extrusion, cutting, and sealing processes should be controlled. Provisions for carefully controlled airflow can protect the product by forcing generated particles outward while preventing any ingress from the adjacent environment. Furthermore, equipment designs that separate the filling zone from the surrounding environment provide additional product protection. Barriers, pressure vacuums, microenvironments, and appropriately directed high velocities of sterile air have been found useful in preventing contamination (Ref. 15). Smoke studies and multi-location particle data can provide valuable information when performing qualification studies to assess whether proper particle control dynamics have been achieved throughout the critical area.

BFS 设备设计通常要求使用专门措施，降低可能污染暴露产品的颗粒水平。与使用 BFS 装置的非制药应用不同，空气质量（即颗粒）控制对无菌药品生产很重要。应当控制塑料

拉伸、切割及封口工艺中产生的颗粒。小心控制的气流通过将内部产生的颗粒排出并防止周围环境颗粒的侵入，保护产品。此外，将分装区与周围环境隔离的设备设计提供了更多的产品保护。在防止污染时，屏障、压力真空、微环境和合适方向的高速气流能够有效预防污染（参考文献 15）。在评估整个关键区域是否已达到合适的动态颗粒控制时，烟雾追踪气流研究和多位点颗粒数据能够提供有用信息。

In addition to suitable design, it is important to establish an adequate preventative maintenance program. For example, because of its potential to contaminate the sterile drug product, the integrity of the cooling, heating and other utility systems associated with the BFS machine should be maintained and routinely monitored.

除设计合理外，重要的是建立充分的预防性维护程序。例如，应当维护与 BFS 设备有关的冷却、加热和其它工程系统的完整性并实施日常监测，因为它们有可能污染无菌产品。

B. Validation/Qualification
验证/确认

Advantages of BFS processing are known to include rapid container closure processing and minimized aseptic interventions. However, only a properly functioning process can realize these advantages. We recommend affording special attention to setup, troubleshooting of equipment, and related aseptic personnel procedures. Equipment sterilization, media fills, polymer extrusion/sterilization, product-plastic compatibility, forming and sealing integrity, and unit weight variation are among the key issues to address in validation and qualification studies.

BFS 工艺的优势包括：快速容器密封加工和最小化无菌干预。然而，只有恰当运作的工艺才能实现这些优势。我们建议特别注意设备的开机、故障排除，以及有关的无菌操作程序。设备灭菌、培养基灌装、塑料粒子吹塑/灭菌、产品与塑料的相容性、成形和密封的完整性和装量的变化等等，都是验证和确认研究的重要内容。

Data gathered during such studies should ensure that BFS containers are sterile and, if used for parenteral drugs, nonpyrogenic. This can generally be achieved by validating that time temperature conditions of the extrusion process are effective against endotoxin or spore challenges in the polymeric material.

在这些研究中收集的数据应当保证 BFS 容器是无菌的，如果是胃肠道外用药，还应当是无热原的。可以通过针对去除聚合物材料的内毒素或孢子的验证确定拉伸工艺的时间温度条件。

The choice of appropriate polymer material for a BFS operation includes assessing if a material is pharmaceutical grade, safe, pure, and passes appropriate criteria (Ref. 17) for plastics. Polymer suppliers should be qualified and monitored for raw material quality.

BFS 操作时聚合物材料的恰当选择包括评估材料是否达到药用水准，是否安全，是否达到纯度标准并符合恰当的塑料指标。（参考文献 17）聚合物供应商应当经过确认，并监控其原材料质量。

C. Batch Monitoring and Control
批监测和控制

Various in-process control parameters (e.g., container weight variation, fill weight, leakers, air pressure) provide information to monitor and facilitate ongoing process control. It is essential to monitor the microbial air quality. Samples should be taken according to a comprehensive sampling plan that provides data representative of the entire filling operation. Continuous monitoring of particles can provide valuable data relative to the control of a blow-fill-seal operation.

不同的中间控制参数（如：容器重量差异、分装重量、漏洞、气压）提供了监控和方便过程控制的信息。应当监视空气微生物质量。应当根据完整的取样计划取样，以便数据代表整个分装操作过程。连续的颗粒监测可以提供与吹—灌—封操作控制相关的数据。

Container closure defects can be a major problem in control of a BFS operation. It is critical that the operation be designed and set-up to uniformly manufacture integral units. As a final measure, the inspection of each unit of a batch should include a reliable, sensitive, final product examination that is capable of identifying defective units (e.g., *leakers*). Significant defects due to heat or mechanical problems, such as wall thickness, container or closure interface deficiencies, poorly formed closures, or other deviations should be investigated in accordance with §§211.100 and 211.192.

在 BFS 操作控制中，容器密封缺陷可能会是一个很大的问题。关键是设计和生产出一致的完整的单元。最后，每批的成品检查中应当包括能够可靠、灵敏的鉴别每一单元的缺陷（如漏洞）。由于热和机械问题所引起的重大缺陷，象壁厚、容器或密封接口的缺陷、成形失败的密封、或其它偏差，都应当根据§§211.100 和 211.192 进行调查。

APPENDIX 3: PROCESSING PRIOR TO FILLING AND SEALING OPERATIONS
附录 3： 分装和封口前的加工

The purpose of this appendix is to supplement the guidance provided in this document with information on products regulated by CBER or CDER that are subject to aseptic processing at points early in the manufacturing process, or that require aseptic processing through the entire manufacturing process because it is impossible to sterile filter the final drug product. The scope of this appendix includes aseptic processing activities that take place prior to the filling and sealing of the finished drug product. Special considerations include those for:

此附录的目的是补充在本指南中由 CBER 或 CDER 所管理产品信息，所述产品在生产工艺的更早阶段使用无菌加工，或者在整个生产过程中使用无菌加工，因为无法对成品进行无菌过滤。此附录的范围包括在成品分装和密封前的无菌工艺活动。特别的考虑包括：

A. Aseptic processing from early manufacturing steps
从更早生产步骤开始的无菌工艺

Some products undergo aseptic processing at some or all manufacturing steps preceding the final product closing step. With other products, there is a point in the process after which they can no longer be rendered sterile by filtration. In such cases, the product would be handled aseptically at all steps subsequent to sterile filtration. In other instances, the final drug product cannot be sterile-filtered and, therefore, each component in the formulation would be rendered sterile and mixed aseptically. For example, products containing aluminum adjuvant are formulated aseptically because once they are alum adsorbed, they cannot be sterile-filtered.

有些产品在成品生产完成前的部分或所有生产步骤都需要无菌加工。而其它产品，在某个工艺步骤后，不能再通过过滤灭菌。在这样的情况下，在无菌过滤后的所有阶段，产品都应当无菌处理。在其它情况下，成品不能无菌过滤，因此，配方中的每一个成分都应当灭菌后在无菌条件下混合。比如：包含氢氧化铝佐剂的产品在无菌条件下配制，因为一旦进行铝吸附，它们就不能够再进行无菌过滤。

When a product is processed aseptically from the early stages, the product and all components or other additions are rendered sterile prior to entering the manufacturing process. It is critical that all transfers, transports, and storage stages be carefully controlled at each step of the process to maintain sterility of the product. In some cases, bulk drug substances or products should be tested for sterility.[24]

当产品从早期阶段采用无菌加工时，产品、所有成分或其他添加物在进入生产加工前都应当灭菌。关键的是小心控制每个工艺步骤的所有转移、转运和贮存阶段，以维持产品的无菌性。在有些情况下，应当测试半成品物料或产品的无菌性。[24]

[24] See 21 CFR 610.12 for general biological product standards for sterility.

[24] 参照 21CFR610.12 生物制品通用无菌性标准。

Procedures (e.g., aseptic connection) that expose a product or product contact surfaces should be performed under unidirectional airflow in a Class 100 (ISO 5) environment. The environment of the room surrounding the Class 100 (ISO 5) environment should be Class 10,000 (ISO 7) or better. Microbiological and airborne particle monitoring should be performed during operations. Microbial surface monitoring should be performed at the end of operations, but prior to cleaning. Personnel monitoring should be performed in association with operations.

暴露产品和产品接触表面的操作（如：无菌连接）应当在 100 级(ISO 5)环境层流条件下操作。100 级(ISO5)环境周围的房间环境应当符合万级（ISO 7）或更高标准。应当在操作期间监测微生物和尘埃粒子。在操作后、清洁前应当监测表面微生物。人员监控应当根据项目操作而进行。

Process simulation studies covering the steps preceding filling and sealing should be designed to incorporate all conditions, product manipulations, and interventions that could impact on the sterility of the product. The process simulation, from the early process steps, should demonstrate that process controls are adequate to protect the product during manufacturing. These studies should incorporate all product manipulations, additions, and procedures involving exposure of product contact surfaces to the environment. The studies should include worst-case conditions such as maximum duration of open operations and maximum number of participating operators. However, the process simulations do not need to mimic total manufacturing time if the manipulations that occur during manufacturing are adequately represented.

包括分装和密封之前步骤的工艺模拟研究应当加入有可能影响产品无菌性的所有条件、产品生产和干预。从早期加工步骤开始的工艺模拟应当证明工艺控制足以在生产期间保护产品。这些研究应当加入所有涉及产品接触表面暴露于环境的产品操作、添加和程序。这些研究应当包括最差情况，例如开放式操作时间最长，以及参与的操作人员数量最多的情况。然而，如果已经充分模拟生产过程中的操作，那么工艺模拟不需要模仿整个加工时间。

It is also important that process simulations incorporate storage of sterile bulk drug substances or product and transport to other manufacturing areas. For instance, there should be assurance of bulk vessel integrity for specified holding times. The transport of sterile bulk tanks or other containers should be simulated as part of the media fill. Please refer to Section IX.A for more guidance on media simulation studies. Process simulation studies for the formulation stage should be performed at least twice per year.

重要的是工艺模拟应当加入无菌半成品物料或产品的贮存及到其它生产区域的转运。如：应当保证半成品容器在特定贮存时间内的完整性。无菌半成品罐或其它容器的转运应当作为培养基灌装的一部分来模拟。参照第 9 部分 A 关于培养基模拟研究的更多指南。配制阶段的工艺模拟研究应当至少一年进行 2 次。

B. Aseptic processing of cellular therapy products and cell-derived products
细胞疗法产品和细胞产品的无菌工艺

Cellular therapy and some cell-derived products (e.g., lysates, semi-purified extracts) represent a subset of the products that cannot be filter-sterilized and therefore undergo aseptic manipulations throughout the manufacturing process. Where possible, closed systems should be used during manufacturing. Cellular therapy products often have short processing times at each manufacturing stage, particularly between the harvest, formulation of the final product, and product release. These products are frequently released from the manufacturing facility and administered to patients before final product sterility testing results are available. In situations where results of final sterility testing are not available before the product is administered, additional controls and testing should be considered. For example, additional sterility tests can be performed at intermediate stages of manufacture, such as after the last manipulation of the product prior to harvest. Other tests that may indicate microbial contamination, such as microscopic examination, Gram stain (or other bacterial and fungal stain), and endotoxin testing should be performed and meet acceptance criteria prior to product release.

细胞疗法产品和一些细胞衍生产品（如： 溶胞产物、半纯化提取物）代表不能无菌过滤的部分产品，因此，需要在整个生产过程中进行无菌操作。如果有可能，生产过程中应当使用封闭系统。细胞疗法产品通常在每个生产阶段有较短的加工时间，尤其是在成品收获、成品配制和产品放行之间。这些产品通常在得到产品无菌性测试结果前，从生产厂家放行并给予患者。如果在给予产品前未得到最终无菌测试结果，那么应当考虑更多的控制和测试。例如：在生产的中间过渡阶段应当进行额外的无菌测试，象在成品出来前给产品进行最后的操作。指示微生物污染的其它测试，例如显微镜镜检、格兰氏染色(或其它细菌和真菌染色)和内毒素检测，应当在产品放行前进行并达到合格标准。

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Contains Nonbinding Recommendations

RELEVANT GUIDANCE DOCUMENTS

Some relevant FDA guidance documents include:

- Guidance for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
- Guideline for Validation of Limulus Amebocyte Lysate Test as an End Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices
- Guide to Inspections of Lyophilization of Parenterals
- Guide to Inspections of High Purity Water Systems
- Guide To Inspections of Microbiological Pharmaceutical Quality Control Laboratories
- Guide To Inspections of Sterile Drug Substance Manufacturers
- Pyrogens: Still a Danger; (Inspection Technical Guide)
- Bacterial Endotoxins/Pyrogens; (Inspection Technical Guide)
- Heat Exchangers to Avoid Contamination; (Inspection Technical Guide)
- Compliance Program Guidance Manual 7356.002 A, Sterile Drug Process Inspections
- ICH Q5A, Guidance on Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- See also the draft guidance Container and Closure Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, which was issued in 1998. Once final, it will represent the Agency's thinking on this topic.

GLOSSARY
词汇表

Air lock- A small room with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an aseptic processing airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area.

气闸 – 带连锁门的小房间，用于保持临近房间之间的气压控制(通常所述临近房间的洁净级别不同)。无菌工艺气闸的目的是排除从较低级别区域的尘埃粒子和微生物污染侵入。

Alert Level- An established microbial or airborne particle level giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are always lower than action levels.

警戒限 –微生物或尘埃粒子的某个水平，对从正常的操作条件可能的偏离作出早期预警，超过警戒限的事件需要详细审查和追踪以发现可能的问题。警戒限总是比行动限低。

Action Level- An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

行动限-微生物或尘埃粒子的某个水平，超过行动限的事件需要合适的调查，并根据调查制定纠正行动。

Aseptic Manufacturing Area- The classified part of a facility that includes the aseptic processing room and ancillary cleanrooms. For purposes of this document, this term is synonymous with "aseptic processing facility" as used in the segregated segment context.

无菌生产区域—厂房内有级别的部分，包括无菌操作房间和辅助洁净室。在本指南中，该术语与各个部分内使用的"无菌加工设施"同义。

Aseptic Processing Facility- A building, or segregated segment of it, containing cleanrooms in which air supply, materials, and equipment are regulated to control microbial and particle contamination.

无菌加工设施-包括洁净室的建筑或其隔离部分，其中空气供应、物料和设备符合特定标准以控制微生物和尘埃粒子污染。

Aseptic Processing Room- A room in which one or more aseptic activities or processes is performed.

无菌加工室- 进行一项或多项无菌活动或加工的房间。

Asepsis- A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbiological contamination of the exposed sterile product.

无菌-通过使用无菌工作区域、并采取措施预防暴露无菌产品受到微生物污染而达到的一种控制状态。

Bioburden- The total number of microorganisms associated with a specific item prior to sterilization.

生物负荷-灭菌前与具体物品有关的微生物总数量。

Barrier- A physical partition that affords aseptic processing area (ISO 5) protection by partially separating it from the surrounding area.

屏障-通过将无菌加工区域(ISO 5)与周围区域部分分开而提供保护的物理分隔。

Biological Indicator (BI)- A population of microorganisms inoculated onto a suitable medium (e.g., solution, container or closure) and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process. The *challenge microorganism* is selected based upon its resistance to the given process. Incoming lot D-value and microbiological count define the quality of the BI.

生物指示剂（BI）- 接种到合适的培养基(如溶液、容器或密封)中的微生物群体，并将其放置到合适的灭菌器装载位置，测定物理或化学过程灭菌循环的功效。微生物种类的选择基于它对既定工艺的抵抗力。该批 D 值和微生物计数决定 BI 的质量。

Clean Area- An area with defined particle and microbiological cleanliness standards.

洁净区域—符合规定的尘埃粒子和微生物洁净级别标准的区域。

Cleanroom- A room designed, maintained, and controlled to prevent particle and microbiological contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.

洁净室—设计、维护及受控制以防止药品受到尘埃粒子和微生物感染的房间。这个房间是指定的，可重复性达到合适的空气洁净等级。

Component- Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the final drug product.

成分—在药品生产中使用的原料,包括那些可能不在成品中出现的原料。

Colony Forming Unit (CFU)- A microbiological term that describes the formation of a single macroscopic colony after the introduction of one or more microorganisms to microbiological growth media. One colony forming unit is expressed as 1 CFU.

集落形成单位(CFU)--微生物术语，描述在将一个或多个微生物接种到微生物培养基后形成的单个肉眼可见集落。一个集落形成单位表示为 1CFU。

Critical Area - An area designed to maintain sterility of sterile materials. Sterilized product, containers, closures, and equipment may be exposed in critical areas.

关键区域-设计用于维持无菌材料的无菌性的区域。灭菌后的产品、包装和设备可能暴露于关键区域。

Clean Zone- See Clean Area.

洁净区-见洁净区域

Critical surfaces- Surfaces that may come into contact with or directly affect a sterilized product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.

关键表面-接触或直接影响灭菌产品或其容器或密封的表面。在开始生产操作前对关键表面灭菌，并在工艺过程中维持无菌性。

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

消毒----通过杀孢子的化学剂消除活体生物负荷的工艺。

Disinfection- Process by which surface bioburden is reduced to a safe level or eliminated. Some disinfection agents are effective only against vegetative microbes, while others possess additional capability to effectively kill bacterial and fungal spores.

消毒—将表面生物负荷降到安全水平或去除的工艺。有些消毒剂只有效针对低营养要求微生物，而其它消毒剂还能有效杀死细菌和真菌孢子。

Depyrogenation- A process used to destroy or remove pyrogens (e.g., endotoxin).

除热原---用于破坏或除去热原(如：内毒素)的工艺。

D value- The time (in minutes) of exposure at a given temperature that causes a one-log or 90 percent reduction in the population of a specific microorganism.

D 值---在规定温度下导致特定微生物群体减少 1 log 或 90%的暴露时间（以分钟计）。

Dynamic- Conditions relating to clean area classification under conditions of normal production.

动态—在正常生产条件下与洁净区域分级相关的条件。

Endotoxin- A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.

内毒素—在细菌细胞壁中存在的热原性产品（如： 脂多糖）。内毒素可以导致接受注射的患者从发热到死亡的反应。

Gowning Qualification- A program that establishes, both initially and on a periodic basis, the capability of an individual to don the complete sterile gown in an aseptic manner.

着装确认---从一开始就建立并定期检查的人员完成完整无菌着装的程序。

HEPA filter- High efficiency particulate air filter with minimum 0.3 μm particle retaining efficiency of 99.97 percent.

HEPA 滤器---高效空气颗粒过滤器，对 0.3μm 颗粒的保留效率至少为 99.97%。

HVAC- Heating, ventilation, and air conditioning.

HVAC---取暖、通风和空调。

Intervention- An aseptic manipulation or activity that occurs at the critical area.

干预---在关键区域出现的无菌操作或活动。

Isolator- A decontaminated unit, supplied with Class 100 (ISO 5) or higher air quality, that provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding cleanroom air and personnel). There are two major types of isolators:

隔离装置—一种经过消毒的单元，提供 100 级(ISO5)或更高空气质量，提供完全、持续的内外环境之间的隔离（如： 周围洁净室空气和工作人员等等）。隔离装置主要有两种类型：

> *Closed isolator systems* exclude external contamination from the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.

封闭式隔离系统：通过无菌连接到辅助设备完成物料转移，从而排除外部污染，而不是使用连接到外部环境的开口。封闭式系统在操作期间保持密封。

> *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.

开放式隔离系统：在操作期间，通过一个或多个开口，允许连续的、或半连续的材料进出。 开口的设计和建造可以防止外部污染进入隔离装置。

Laminar flow- An airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight line vector.

层流—从直线向量的开头到末端，以单一方向、水平层流和恒定速度移动的气流。

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

操作人员---参加无菌工艺操作如开机、分装、维护的工作人员，或其它与无菌生产线有关的人员。

Overkill sterilization process- A process that is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D value of 1 minute.

过度灭菌工艺---足以使微生物降低至少 12 log、最小 D 值为 1 分钟的工艺。

Pyrogen- A substance that induces a febrile reaction in a patient.

热原----在患者体内引起发热反应的物质。

Sterile Product- For purposes of this guidance, *sterile product* refers to one or more of the elements exposed to aseptic conditions and ultimately making up the sterile finished drug product. These elements include the containers, closures, and components of the finished drug product.

无菌产品---在本指南中，无菌产品是指暴露于无菌状态并最终组成无菌成品的一种或多种元件。这些元件包括容器、密封和成品的成分。

Sterilizing grade filter- A filter that, when appropriately validated, will remove all microorganisms from a fluid stream, producing a sterile effluent.

灭菌级过滤器—经验证证明能从流体中去除所有微生物、产生无菌液体的过滤器.

Quality Control Unit- An organizational element with authority and responsibility as defined by 211.22.

QC 部门—具有如 211.22 所规定的权力和责任的机构单位。

Unidirectional flow- An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

单向流—充分而一致的单向气流，它以足够的速度从关键加工或测试区域重复吹走颗粒。

Terminal sterilization- The application of a lethal agent to sealed, finished drug products for the purpose of achieving a predetermined sterility assurance level (SAL) of usually less than 10^{-6} (i.e., a probability of a nonsterile unit of greater than one in a million).

最终灭菌—将致死剂应用于密封的成品上，达到通常低于 10^{-6} 的预定无菌保证值(SAL)(即出现非无菌单位的概率少于百万分之一)。

ULPA filter- Ultra-low penetration air filter with minimum 0.3 μm particle retaining efficiency of 99.999 percent.

ULPA 滤器---极低穿透率的空气滤器，0.3μm 颗粒的保留效率至少 99.999%。

Validation- Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

验证—一个有文件和记录的方案，它能高度保证一项专门的工艺过程确实始终如一地生产出符合预定规格及质量标准的产品。

Worst case- A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure.

最差情况---一组最有可能造成工艺或产品失败(与理想状况相比)的包括工艺上限和下限的条件，包括那些在 SOP 中规定的条件。所述条件不一定导致产品或工艺失败。