PDA TECHNICAL REPORT NO. 13 REVISEDFUNDAMENTALS OF AN ENVIRONMENTALMONITORING PROGRAM

技术报告 13：环境监测

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1.0 INTRODUCTION 简介

The purpose of this document is to identify microbiological and particulate control concepts and principles as they relate to the manufacture of sterile pharmaceutical products. It expands substantially upon the first edition of Technical Report No. 13, Fundamentals of a Microbiological Environmental Monitoring Program, published by PDA in 1990. While this publication cannot possibly supplant the wealth of information published on this subject, it provides summary information and appropriate references for the reader to consult, if necessary. The objective was to contemporize the first edition through the utilization of current definitions, recognition of improved environmental monitoring procedures, and equipment. 本文件目的是确定微生物和微粒控制的概念和原则，因为这涉及到无菌药品的生产。文件全称为第13号技术报告第一版，微生物的环境监测计划基础，PDA于1990年出版。尽管本出版物不可能取代题目的信息价值，它提供了读者查阅必要的主要信息及相关参考。其目的是通过使用当前定义，改善后的环境监测程序和设备来与第一版同步。

This document should be considered as guidance; it is not intended to establish any mandatory or implied standard. ***此文件应作为指南；而不是建立任何强制或隐含的标准。***

The task force consisted of members representing global companies, to ensure that the methods, terminology, and practices reflect the procedures utilized globally. Technical reviews were performed by some of the more prominent environmental monitoring scientists in the world today. 工作团队由代表全球性公司的成员组成，以确保方法，术语和规程反映了全球范围内使用的程序。技术审查由一些全球重要的环境监测科学家进行。

This document serves as a source on clean room environmental test methods, and although some non-viable particulate and endotoxin testing data are included, its primary focus is microbiological control. The concepts for sterile product manufacturing are the most stringent application, but these concepts can also be applied to non-sterile product manufacture. The focus is environmental monitoring as it relates to facility control and compliance. This document was compiled to aid in setting up a program that is meaningful, manageable, and defendable. 这份文件作为洁净室环境测试方法的来源，虽然包括一些非活性微粒和内毒素检测数据，其主要目的是微生物控制。无菌产品生产的概念是最严格的应用程序，但这些概念也适用于非无菌产品的生产。重点是环境监测，因为它涉及到设施的控制和遵守。编写本文件是为了协助建立一个有意义，易于管理且合理的程序。

In order to ensure a consistently acceptable production environment, a comprehensive environmental control program should be supported by: (a) sound facility design and maintenance, (b) documentation systems, (c) validated/qualified sanitization/disinfection procedures, (d) reliable process controls, (e) good housekeeping practices, (f) effective area access controls, (g) effective training, certification/qualification and evaluation programs and (h) quality assurance of materials and equipment. 为了确保持续可接受的生产环境，全面的环境控制计划应当得到以下支持：（a）合理的设施设计和维修，（b）文件系统，（c）经验证/合格的杀菌/消毒程序，（d）可靠的工艺控制，（e）良好的车间管理规程，（f）有效面积的访问控制，（g）有效的培训，认证/确认和评价程序和（h）材料和设备的质量保证。

Environmental surveillance is a tool utilized to evaluate the effect of controls on the manufacturing environment. A process to assess the clean room and other controlled environments of a pharmaceutical facility can serve as an adjunct to the sterility

assurance program for the microbial quality of drugs. The items addressed in this document include definitions, standards, surveillance support systems, system surveillance, validation systems, appendices of definitions and typical frequencies and levels, and a bibliography. 环境监测是用于评价对生产环境控制效果的工具。评估洁净室和其他制药设备受控环境的工艺可作为对药物的微生物质量无菌性保证的辅助方法。本文件涉及的项目包括定义，标准，监督支持系统，系统监控，验证系统，定义和典型频率和等级附录和参考书目。

2.0 ENVIRONMENTAL CLASSIFICATIONS 环境分级

The environmental monitoring program should be designed and implemented based on sound scientific principles, the need for and the utility of the collected data, and in conformance with the regulatory requirements of the government agencies regulating the manufacturing site. Personnel administering environmental monitoring programs should be familiar with a variety of regulatory schemes if they are to be successful in serving the United States and International product markets. Efforts at harmonization are underway, and it is possible that many of the differences in the requirements for monitoring programs may disappear as the countries and organizations involved come to some agreement on the overall approach to be taken. Therefore, it is important to keep up to date on the requirements for the different countries in which the product will be sold. 环境监测程序应根据合理的科学原则，收集到的数据的需求和使用进行设计和执行，符合政府机构监管生产现场的要求。如果人事管理环境监测计划能够成功服务于美国和国际产品市场，应熟悉不同的管理计划。目前正在努力协调，检测计划的要求的差异可能会消失，因为涉及的国家和组织正在协调获得统一的方法。因此，应及时更新产品销往国的要求。

This will ensure that the established program meets the monitoring requirements of each country. If the intent is to serve both the United States and the International markets, the most stringent requirements should be evaluated as the basis of an environmental monitoring program. 这将确保既定的程序符合每个国家的监测要求。如果目的是为服务美国和国际市场，最严格的要求应作为环境监测计划的基础进行评估。

This section compares published environmental classifications for environmental monitoring in the United States and the European Union. Although these publications are similar in many respects, there are important differences among them in terms of the information each provides. 本节比较公布的美国和欧盟环境检测的分级。虽然这些刊物在许多方面是相似的，其提供的信息仍有重大分歧。

Federal Standard 209E establishes airborne particulate cleanliness classes categorized as Class M 1 through M 7 (SI names). All of the classifications can be applied to particles > 0.5µm, while other particle sizes, e.g., 0.1, 0.2, 0.3 and 5µm, utilize only some of the classifications. In the United States, the pharmaceutical industry classifies production areas as Class 100, 10,000 and 100,000 (M 3.5, M 5.5 and M 6.5, respectively) based on particles > 0.5µm, the classification reflecting the number of particles per cubic foot. It should be noted that the Institute for Environmental Sciences and Technology (IEST) has recommended that Federal Standard 209E be retired by the end of 2001 as a result of the publication of the ISO 14644-1 and 14644-2 documents. 美国联邦标准209E规定空气中微粒洁净度M1到M7级。所有分级适用于> 0.5µm的粒子，其他粒子，如0.1、0.2、0.3和5µm，仅使用某些分级。在美国，制药行业根据> 0.5µm的粒子将生产区分为100级，10,000级和100,000级（分别为M3.5，M5.5和M 6.5），分类反映了每立方米微粒数量。应当指出，环境科学与技术（IEST）研究所建议，ISO 14644-1和14644-2文件出版后，美国联邦标准209E可于2001年底暂停使用。

FDA's 1987 "Guideline on Sterile Drug Products Produced by Aseptic Processing" discusses environmental requirements for critical areas (Class 100), in which sterile drugs are exposed to the environment. This document also includes specifications for viable airborne monitoring for Class 10,000 and Class 100,000 areas. Viable and non-viable guidance is provided. FDA的1987年"关于无菌加工生产的无菌药品指南"讨论了关键区域（100级）的环境要求，其中无菌药物暴露于环境。本文件还包括了10,000级和100,000级区域的活性空气的监测说明。提供了活性和非活性监测指南。

USP general information chapter <1116> "Microbial Evaluation and Classification of Clean Rooms and Other Controlled Environments" proposes limits for clean room levels, including air, surfaces, and personnel working within the clean area. The chapter includes three classifications that would supplement the current categories based on non-viable particulate limits. 美国药典的一般信息章节"1116""微生物评估和洁净室分级及其他受控环境"提出了洁净室级别的限制，包括洁净区空气，表面和人员工作。本章包括三个分类，将根据非活性颗粒极限补充现行分级。

In the European Union, *The Rules Governing Medicinal Products in the European Union, (Vol. IV: Good manufacturing practice for medicinal products)* include an air classification system in Annex 1 under the heading "Manufacture of Sterile Medicinal Products." Air quality is classified alphabetically as Grade(s) A through D, with Grade A being the cleanest. Associated with each respective grade is the maximum allowable number of particles per cubic meter. 在欧盟，欧盟药品细则（第四卷：药品良好生产质量管理规范），包括附件1"无菌产品生产"中的空气分级系统。空气质量按字母顺序分为A级D级，A级洁净度最高。与每个等级相关的是每立方米微粒最大允许数量。

In addition to these publications, additional guidance is available through the International Organization for Standardization (ISO) which is a world-wide federation of national standard bodies. The work of preparing international standards is normally carried out through ISO technical committees. ISO/TC 198 provides *Guidance for Sterilization of Health Care Products* and ISO/TC 209 provides *Guidance for the Classification of Airborne Particulate for Clean Rooms and Associated Controlled Environments.* Copies of these documents can be obtained from American National Standards Institute (ANSI). 除了这些出版物，国际标准化组织（ISO）有更多的指南，ISO是一个世界标准机构的联盟。制订国际标准的工作通常由ISO的技术委员会进行。ISO/ TC 198提供保健品无菌性指南，ISO/ TC 209提供洁净室和相关受控环境中空气粒子分级指南。这些文件的副本可从美国国家标准学会（ANSI）获得。

It should be noted that all classifications have a direct counterpart in the documents prepared by other international groups. Tables 1 through 3 summarize and compare these specifications. 应当指出，所有分级在其他国际组织编写的文件中有直接对应。表1至3总结并比较了这些规范。

3.0 SURVEILLANCE SUPPORT 监视支持

The data should be collected in a manner that is in conformance with Current Good Manufacturing Practices (CGMP). CGMP states that the personnel supervising the environmental monitoring program should be competent in the scientific discipline and have appropriate training and authority. Equipment used should be calibrated, systems should be appropriately validated, media should be properly prepared, and all operational procedures should be written and followed. 这些数据应当按照现行良好生产规范（CGMP）进行收集。CGMP规定，监督环境监测计划的人员应有科学学科的能力，

并有相关培训和权威。使用的设备应进行校准，系统应适当验证，介质应适当制备，应编写并执行所有运行程序。

Procedures should include appropriate controls to support their use. Cleaning, sanitization/disinfection, site selection, and frequency of testing are key components to a good environmental monitoring program. Alert and action levels should be based on individual sample sites, but one may also choose to specify alert level and action levels based on the number of excursions in one area/system for one sampling period. Establishment of appropriate alert and/or action levels and a system for monitoring implies that data obtained are subject to continual review and that alert and action decisions are made by designated, authorized personnel qualified to make such decisions. To effectively execute microbiological surveillance support systems, there should be a documented system in place for identifying excursions; in addition, there should be a feedback mechanism for verification of any action taken in response to data. All data should be documented and trended.
程序应包括适当的控制，以支持其使用。清洗，杀菌/消毒，选址，以及测试频率是良好环境监测计划的重要组成部分。报警和行动等级应根据每个样品的位置，但也可以根据一个取样周期内一个区域/系统的偏差数指定警戒水平和行动水平。适当警报和/或行动水平和监测体系的建立意味着获得的数据需不断审查，警报和行动由指定的授权人员做出决定。为了有效地执行微生物监测支持系统，应该有一个记录的在线系统识别偏差；此外，应有对数据响应行动进行确认的反馈机制。所有数据应记录并分析趋势。

3.1 Cleaning and Sanitization/Disinfection 清洗和杀菌/消毒

Implementation of cleaning and sanitization procedures is a critical component of overall facility control. Environmental monitoring data are used in determining the effectiveness of these procedures. It is common knowledge that the ideal sanitizer does not exist. Sanitizers that are effective against vegetative cells may be ineffective against spores. Sanitizers or disinfectants that are effective against spores are usually corrosive to equipment (e.g., acidified bleach on stainless steel) and should be used sparingly on an as-needed basis. Selection of sanitizers may include evaluation of required contact time, type of microorganisms that are to be eliminated, confirmation of efficacy, type of surface to be treated, toxicity, residue, and means of application. Validation of established cleaning and sanitization procedures should demonstrate microbial reduction. The procedures also ensure the effectiveness of removal of product and detergent residue. The goal is to demonstrate that routine sanitization procedures, performed by trained cleaning personnel, consistently result in a level of microbial control suitable for the intended use of the area. Sanitization procedures are verified for the effectiveness of microbial reduction. It is a sound practice to perform challenge testing of the selected sanitizers/disinfectants with isolates routinely recovered by the environmental monitoring program. This establishes the practical effectiveness of the disinfectants.
清洁和杀菌程序的执行是整体设施控制的重要组成部分。环境监测数据可用于确定这些程序的有效性。大家都知道，理想的消毒剂不存在。对营养细胞有效的消毒剂可能对孢子无效。对孢子有效的杀菌剂或消毒剂通常能腐蚀设备（例如，酸化漂白不锈钢），使用时需谨慎。对杀菌剂的选择可能包括评估所需接触时间，将除去的微生物类型，效力确认，将处理的表面类型，毒性，残留以及应用方法。已建立的清洁和消毒程序的验证应证明微生物的减少。该程序还保证了产品和洗涤剂残留去除的效率。目标是证明由经过培训的人员进行的常规消毒程序可使微生物控制水平符合区域目标。确认杀菌程序减少微生物的效率。这是进行已选择消毒剂/灭菌剂挑战性测试的有效规程，分离株通常由环境监测计划复原。这规定了消毒剂的实际效力。

3.2 Sample Site Selection 样品位置选择

Suitable sample sites vary widely depending on the clean room design and manufacturing process. Each process should be carefully evaluated when selecting sampling sites. The primary purpose of sampling should be to provide meaningful interpretable data that can help identify actual or potential contamination problems associated with specific procedures, equipment, materials, and processes. One should be able to sample those sites most likely to result in product contamination if they become contaminated; however, it may be prudent to identify indicator sites that are near, but not in contact with product. 合适的取样位置差异很大，取决于洁净室的设计和生产工艺。选择采样点时，应认真评估每个工艺。取样的主要目的应是提供有意义可解释的数据，可以帮助确定与具体程序，设备，材料和工艺相关的实际或潜在污染问题。应能对最能够导致产品污染的位置；但是，它可能会谨慎确定附近的指示器位置，而不与产品接触。

Factors to consider in selecting sites for routine surveillance are: 日常监测选择位置时要考虑的因素：

1. At which sites would microbial contamination most likely have an adverse effect on product quality? 微生物污染极有可能对产品质量造成不良影响的位置？
2. What sites would most likely demonstrate heaviest microbial proliferation during actual production? 最有可能表现出实际生产过程中微生物扩散最严重的位置？
3. Should site selection involve a statistical design (e.g., following the calculations in Federal Standard 209E) or should site selection be made on the basis of grid profiling? Should some sites for routine monitoring be rotated? 选址是否涉及统计设计（例如，继美国联邦标准209E的计算），或选址是否根据网格计算分析？常规监测的位置是否应轮换？
4. What sites would represent the most inaccessible or difficult areas to clean, sanitize, or disinfect? 哪些位置最难接近或最难清洁，杀菌或消毒？
5. What activities in the area contribute to the spread of contamination? 该区域的哪些活动有助于污染蔓延？
6. Would the act of sampling at a given site disturb the environment sufficiently to cause erroneous data to be collected or contaminate product? Should sampling only be performed at the end of the shift? 在指定位置取样是否会干扰环境，导致收集的数据错误或污染产品？取样是否只能在轮班结束时进行？

Note: There are some considerations applicable to specific types of monitoring; they are described in the individual monitoring sections of this document. *注意：有一些考虑项适用于特定类型的监测，在本文档的监测章节描述。*

To establish routine sample sites, action and alert levels, and testing frequency, one should take into consideration the extent of contact or exposure that each element of the manufacturing environment has with the product. Sites having greater opportunity for contributing bioburden to the product should be sampled and monitored. Product contact sources may include compressed gases, room air, manufacturing equipment, tools, critical surfaces, storage containers, conveyors, gloved hands of personnel, and water. Examples of non-product contact sources may include walls, floors, ceilings, doors, benches, chairs, test instruments, and pass-throughs. 为建立常规取样点，报警和行动等级，测试频率，应该考虑到每个生产环境要素与产品的联系或接触程度。很可能对产品带来生物负荷的位置应进行取样并监测。产品接触源可能包括压缩气体，室内空气，制造设备，工具，关键表面，储存容器，传送带，人员戴手套的手和水。非产品接触源可能包括墙壁，地板，天花板，门，长椅，椅子，测试仪器及传递窗。

It must be recognized, however, that it may not always be practical to select a site at the most critical location. One should consider whether critical site monitoring would actually increase probability of product contamination. Additionally, critical sites may not be monitored if there is a low probability of contamination during processing (e.g., sterilized components which are not manipulated). 然而，必须承认在最关键的位置选择取样点并不实际。应该考虑到关键位置监测是否实际上增加了产品污染的可能性。此外，如果加工过程中污染的可能性低，则不能监测关键取样点（如未操控已消毒组件）。

As pointed out in other sections of this document, there are many considerations in establishing an appropriate site for sampling (e.g., facility design, line configurations, validation data, process, historical data, test methodology, etc.). The sites listed in this section may or may not be applicable to a particular manufacturing process; factors pertaining to site selection are likely to be unique to individual facilities. 正如在本文件的其他部分提出的，建立相关取样位置需考虑到很多方面（例如，设施设计，线路配置，验证数据，工艺，历史数据，测试方法等）。本节中列出的取样点不一定适用于一个特定的生产工艺，位置选择的相关因素对每个设施可能都是独一无二的。

3.3 Sampling Frequency 取样频率

Monitoring requirements may vary widely in the industry depending on several factors including, but not limited to, type of manufacturing process or product, facility/process design, amount of human intervention, use of subsequent terminal sterilization (including sterility test release versus parametric release), and historical profiles of the microbiological environmental data. No single sampling scheme is appropriate for all environments. In addition, changes in sampling frequency, whether temporary or permanent, may be required based on changes in practices, compendial requirements, development of significant microbiological trends, acquisition of new equipment, or nearby construction of rooms or utilities. The key is to select monitoring frequencies that can identify potential system deficiencies. 监测要求根据若干因素可能会有很大区别，包括但不限于，制造工艺或产品类型，设施/工艺设计，人员干扰数量，随后最终灭菌的使用（包括无菌测试放行与参数发布的对比），微生物环境数据的历史概况。没有任何单一的取样计划适用于所有环境。此外，根据规范，药典要求，重要微生物的趋势发展，新设备的购置或附近房间或公用事业建设，可能要求取样频率的变化，不论是暂时的或永久的。关键是要选择可以发现潜在系统缺陷的监测频率。

Examples of sampling sites. 取样点举例

System 系统	Site 位置
• Environmental air (filling line) 环境空气（灌装线）	• Near open and/or filled containers 靠近打开和/灌装的容器
• Room air 房间空气	• Proximal to work area 接近工作区
• Water 水	• Point of use 使用点
• Surface (facility) 表面（设施）	• Floor, door handles, walls, curtains 地面，门把手，墙，窗帘
• Surface (equipment) 表面（设备）	• Filling line, control panels, stopper bowl 灌装线，控制面板，瓶塞料斗
• Compressed air 压缩空气	• Site farthest from compressor 离压缩机最远

	的位置
• Sterility test manifold 曲菌测试支管	• Port closest to vacuum source 最接近真空源的口
• Operator on filling line 灌装线操作员	• Finger impressions, at a minimum 至少是手指印痕
• Laminar air flow (e.g., hood) 空气层流（如层流罩）	• Near high activity areas 靠近高活动区

The test frequency per site may be less frequent than the system or area frequency (e.g., one may choose to rotate sample sites). Test frequencies for batch-related, in-process monitoring may differ from those for routine area monitoring. In many cases, monitoring performed in conjunction with batch production may fulfill the requirements for routine area monitoring. 每个位置的测试频率可能低于系统或区域频率的频繁（例如，可以选择轮换取样点）。批相关的处理中监测的测试频率可能不同于常规区域监测。在许多情况下，与批生产相关的监测可能满足日常区域监测的要求。

Prior to implementing any reduction in frequency, a summary of historical data, along with current and proposed sampling frequencies, should be reviewed and approved by the appropriate Quality Assurance personnel. After reduction, data should be reviewed periodically to determine if the reduced sampling frequency is still appropriate. 减少任何频率前，历史数据总结以及现有和拟议取样频率，应由相关质量保证人员进行审查并批准。减少后，数据应定期审查，以决定减少后的取样频率是否仍适合。

3.4 Alert and Action Levels 报警和行动等级

Environmental monitoring programs may have action levels established based on applicable guidelines and review of historical data. They frequently recommend that alert levels also be established. Some companies also choose to set levels for individual clean rooms or sample sites. Typically, the action levels will be driven by the regulatory or industry guidelines while the alert levels may be driven by historical analysis of the environmental monitoring data. The application of alert and/ or action levels should follow written procedures and be employed in a consistent, non-arbitrary manner. To create consistency in treatment of alert and/or action levels, logical investigatory and/or corrective action steps should be pre-specified. Records should show that any excursion was recognized and that appropriate follow-up occurred. 环境监测程序可能有建立于适用的指南和历史数据审核的行动等级。他们经常建议建立警戒级别。有些公司为每个洁净室或取样位置设立等级。通常情况下，行动等级由规范或工业指南推动，而警戒级别可能由环境监测数据的历史分析推动。警报和/或行动等级的应用都必须按照书面程序并持续不武断地进行。为建立警报和/或行动等级处理的持续性，应预先规定合理的调查和/或纠正行动步骤。记录应表明认识到任何偏离并采取适当的后续行动。

Once alert and/or action levels have been established, they should be periodically reviewed as part of routine trend analysis. They may also be revised to reflect improvements, advances in technology, changes in use patterns, or other changes. 一旦警报和/或行动等级已经确定，应作为常规趋势分析的一部分进行定期审核。也可以进行修订，以反映改善，技术进步，使用方式变更或其他变化。

When no regulatory or industry guidelines are provided, alert and/or action levels may be derived statistically from historical data. An occasional excursion from these

levels is to be expected at frequencies characteristic for the specific mathematical model utilized in their derivation. In some situations, only one level may be employed, with any excursions triggering action. In other instances, a level may be used with a single excursion eliciting an alert/action level response and multiple or sequential deviations requiring action. 当没有提供法规或工业指南时，报警和/或行动等级可能来自于历史数据统计。这些等级的偶尔偏离可能发生于偏离数学模型特有的频率上。在某些情况下，可能只有一个等级，任何偏离可能触发行动。在其他情况下，某个偏离引出警告/行动等级响应及多个或一系列偏差需要行动时可能需要等级。

These levels are conservative measures designed to signal potential or actual drift from historical or design performance characteristics. They are not extensions of product specifications, but are intended to flag changes so that corrective action may be taken before product quality is adversely affected. Not all situations require use of both alert and action levels. 这些级别用于处理信号与历史或设计性能存在潜在或实际漂移的保守措施。他们不是产品规格的扩展，而是用于信号变化，从而在产品质量受到影响前可以采取纠正措施。并非所有情况都需要使用报警和行动等级。

Since there is no consensus as to the best mechanism to use for setting these levels, the following are approaches that have been used successfully within the pharmaceutical industry. Where compendial requirements exist, they supersede the methods used in the following examples. 由于设置这些级别的最好机制没有统一的意见，以下是在制药行业成功的做法。存在药典要求时，则取代以下例子中使用的方法。

a. Cut-off Value Approach 截止值法

All the test data for a particular site are arranged in a histogram and the alert and action levels are set at values whose monitoring results are respectively 1% and 5% higher than the level selected. Other percentiles may be used in establishing levels. A variation is to take the last 100 monitoring results and use the 95th and 99th percentile values as the alert and action levels. 所有的指定位置的测试数据排列在一个柱状图中，警报和行动等级设定为监测结果分别高于所选等级1%和5%的值。其他百分数可用于建立等级。不同是取最后100个监测结果，使用第95和第99个百分值作为报警和行动等级。

b. Normal Distribution Approach 正态分布法

This approach is best used for high counts only (a Poisson distribution is used for low counts). The mean and standard deviation of the data are calculated and the alert and action levels are set at the mean plus two and three times the standard deviation, respectively. 这种方法最适用于高数目（泊松分布用于低数目）。计算数据的均值和标准差，警报和行动等级分别设为平均值加上两倍及三倍的标准差。

c. Non-parametric Tolerance Limits Approach 非参数容许极限法

In this approach, alert and action limits are set using non-parametric (distribution free) methods. This is valuable for environmental monitoring data that typically is not normally distributed, i.e., exhibits high levels of skewness towards zero counts. For the alert limit, the tolerance limit was set at a level of y = 0.95 and P = 0.95. The action limit resulted from a tolerance limit set at y =0.95 and P = 0.99. These limits allow us to assert with confidence at least 95% that 100(P) or 99% of a population lies below the value, depicted by the stated limits for the respective data. For a discussion of this non-parametric procedure, see "Practical Nonparametric Statistics," 3rd edition, by W. J. Conover, page 150. 在这种方法下，警报和行动等级通过非参数（独立分布）方法设定。这对通常为非正态分布的环境监测数据是有价值的，即对零计数表现高等级偏离。对于报警极限，容许极限设为y = 0.95，P = 0.95。来自容许极限的行动极限设为y = 0.95，P = 0.99。这些限制使我们相信至少95%的100（P）或99%总数在这

个值之间，通过各自数据的极限描述。关于此非参数程序的讨论，请参阅"实用非参数统计"第3版，由WJ康诺弗编著，第150页。

Other models based on negative binomial, Poisson, Weibull, or exponential distributions are possible. It may be appropriate to determine the model that best fits the data and use that model to set the levels. Typically, contamination in strictly controlled environments does not fall within a normal distribution. Environmental monitoring data may be evaluated to determine the suitability of the approaches to level setting. 其他模型可能是根据负二项分布，泊松，威布尔或者指数分布。可能确定最适合数据的模型是适当的，并使用该模型设定等级。通常，在严格控制环境的污染不属于正态分布。可能评估环境监测数据以确定等级设置方法的适用性。

3.5 Data Management (Data Collection, Analysis, Approach, and Interpretation) 数据管理（数据收集，分析，处理方法和解释）

Routine review and analysis of environmental monitoring data is essential to aid in the interpretation of process stability and assess overall control performance. Management should be kept abreast of trends and the subsequent state of operations within their facilities. 常规审查和环境监测数据的分析对于协助工艺稳定性解释并评估整体控制性能是必要的。管理应与设施趋势和运行的随后状态同时进行。

Based on the large number of samples tested by a given facility, a computer-based data tracking system is recommended. Prior to implementation, all database applications used should be validated/qualified for specific software applications. 根据规定设施测试的样品数量，建议采用基于计算机的数据跟踪系统。在执行之前，应验证/确认所有数据库应用程序的具体软件应用情况。

3.5.1 Data Collection 数据采集

Routine data may be pooled into a designated database in a consistent record format. The record format should include (at a minimum): monitoring date, specific sampling locations, sampling methods, colony forming units (CFU) or non-viable count results, identification performed, product lot information, and current action level. A manual data entry or image scanner system with advantages of speed and accuracy can be used to populate tables. Data integrity must be verified prior to analysis. 常规数据可能会按统一的记录格式集中到指定的数据库中。记录格式（至少）应包括：监测日期，具体的取样地点，取样方法，菌落形成单位（CFU）或非活性的统计结果，鉴别完成，产品批号信息和当前行动等级。人工数据输入或有速度和准确性优势的图像扫描系统可用于填充表。数据完整性测试应在分析前确认。

3.5.2 Data Analysis 数据分析

Trends are often difficult to obtain and recognize, given the low colony forming unit (CFU) result usually obtained with viable environmental monitoring data. Histograms, defined as pictorial graphs characterized by a number of data points that fall within a common frequency, are a valuable tool. Different room classifications with definite requirements will produce different histograms. The CFU spread obtained across a Class 100,000 data set will not be observed in a data set from a Class 100 area. Therefore, each area (or area type) and accompanying data set must be viewed as distinct. A mathematical model could be applied not only with the objective in mind, but also the type of data to be analyzed. 由于低菌落形成单位（CFU）的结果通常与活性的环境监测数据同时获得，因此很难得到并确认趋势。柱状图，定义

为共同频率下一系列数据点形成的图案图表，是一个有价值的工具。明确要求的不同房间分级将产生不同的柱状图。100,000级区的数据集中获得的CFU将不会从100级区数据集获得。因此，每个区（或区类型）和随附的数据集必须被看作是独一无二的。数学模型不仅可以应用到目标中，也能应用到将分析的数据类型中。

Moreover, data collected in Class 10,000 or 100,000 areas tend to assume distributions. A Class 10,000 facility may lend itself to an exponential distribution where the majority of data points can be observed below the mean and thus appear not normally distributed; and a class 100,000 or non-classified area often demonstrates greater variability around the mean with a normal distribution. A Class 100 area distribution may be less obvious where an unsystematic approach, although less powerful, may work best. 此外，10,000级或100,000级收集的数据用于假定分布。A级10,000设施本身可能带来指数分布，大部分数据点都低于平均值，从而出现非正态分布；100,000级或非分级区域通常用正态分布显示更大的均值变量。使用非系统的方法处，100级区的分布可能不那么明显，作用可能不大，但效果可能最好。

The following table provides some examples of different analysis objectives and the associated descriptions of what the analysis may include. 下表提供了一些不同分析目标的例子，及可能包括哪些分析的相关说明。

3.5.3 Data Approach 数据处理方法

The following approach describes a generalized method for data to assess the environmental control: 下面的方法描述了数据的广义方法，以评估环境控制：

a. Determine objective of analysis (e.g., site location alert/action, action level review, management update). 确定分析的目标（例如，选址警报/行动，行动等级审核，管理更新）。

b. Specify data set to be analyzed. 指定将分析的数据

c. Apply data plots such as histograms or pictorial plots to access the basic data and to determine the nature of the distribution, if any. Such data plots can also be used to locate peculiarities such as outliers or patterns. 如存在，使用数据图，如柱状图或图示以评估基础数据并确定分布的性质。这些数据也可用于定位，如异常值或模式。

d. Observe the distribution and proceed with the appropriate mathematical model that best fits the overall objective. If data conform to a specific distribution, a parametric mathematical model may be applied. If the data are not consistent with a particular distribution, then a non-parametric approach may be applicable. 观察分布并继续使用最适合总体目标的相关数学模型。如果数据符合特定分布，可以应用一个参数数学模型。如果数据不符合特定分布，那么非参数方法可能适用。

e. Typically, an action level at the 99th percentile is employed. Consistent with the action level at the 99th percentile are the following mathematical models. Models can only be applied if the character of the data assumes a definite distribution. 通常使用第99个百分数的行动等级。与第99个百分数的行动等级一致的为以下数学模型。数据特征呈现特定分布时才能使用模型。

Action level estimate for a data set reflecting an exponential or non-normal distribution = 4.6 x (mean CFU) 数据集预估的行动等级反映指数或非正态分布= 4.6 ×（平均CFU）

Action level estimate for a data set reflecting a normal distribution = 2.33 a + (mean CFU) 数据集预估的行动等级反映正态分布= 2.33a +（平均CFU）

Note: When the action level is determined at the 99th percentile, an occasional excursion is expected due to the model applied. 注：当第99个百分数确定为行动等级，偶尔偏差则由于使用的模型导致。

f. Regardless of the statistical model chosen, the analytical method should be consistent with the data and documented in the data summary along with results. 不管选定什么统计模型，分析方法应符合数据并与结果一起记录在数据汇总中。

Examples of possible analysis objectives and possible report descriptions. 可能的分析目标和报告说明举例

Analysis Objective 分析目标	**Report Description** 报告说明
Using alert/action results to determine "corrective action" 用报警/行动结果确定"纠正行动"	Plot data over time to observe trends and process variation. Process control charts can be a useful tool. Modify cleaning, process or equipment. 在一段时间内标记数据，观察趋势和工艺变化。工艺控制图可以成为一个有用的工具。修改清洗，工艺或设备。
Determine appropriateness of current alert/action levels 确定当前报警/行动等级的适宜性	Calculate action level from historical data and compare to current. Action level derivations may be applied to adjust for more reasonable levels that are achievable with current operating procedures. (This may not always be possible if regulatory requirements are present.) 计算历史数据的行动等级并与当前对比。行动等级偏差可能用于调节更多通过当前操作程序达到的合理等级（如果不存在法规要求，则不一定可能。）
Management update, with periodic reporting. Annual report to comprise data summaries as well as process action level reviews 管理更新，定期报告。年度报告，包括数据的汇总，以及工艺行动等级审核	Routine report may include all monitored facilities/personnel data summaries with a list of current action levels, list of outliers and clusters or patterns, identifications, result ranges, sample totals, new action level derivations, and description of statistical method used for any calculations applied. Characterizations should also be included. Process capability and process control charts are often useful in assessing control/variation. 定期报告可能包括所有监控设施/人员数据总结，包括当前行动等级列表，异常值，集群或模式列表，标识，结果范围，样品总量，新的行动等级偏差和任何计算的数据方法说明。特征也应包括在内。加工能力和工艺控制图通常用于评估控制/变更。
Determine process capability 确定工艺兼容性	Perform a quality study to determine specifications. Calculate action levels based on historical data. Histograms and process capability charts are useful tools. 执行质量研究，以确定规格。根据历史数据计算行动等级。柱状图和加工能力图是有用的工具。

3.5.4 Data Interpretation 数据解释

Data generated should be summarized and evaluated to determine whether the production environment is in a state of control. Statistical process control is one method of performing this evaluation. 应总结并评估生成的数据，以确定生产环境是否处于控制状态。统计工艺控制是进行此评估的一种方法。

Trends may show a gradual increase or decrease in the overall counts observed over time, or a change in flora or counts on several plates of a particular area on a given day. Interpretation of the impact of a significant fluctuation in counts or a change in flora should be based on the experienced judgment of a qualified person. 趋势可能

会在观察时间内显示总数的逐渐增加或减少，或在指定某天特定区域的几块板上的菌落或计数变更。计数的重大波动或菌落变更的影响应由有经验的人员判断。

Some considerations for assessing process state of control are listed below: 评估工艺控制状态的几点考虑如下

a. In assessing environmental monitoring process reliability, derived action levels reflecting higher values than those currently imposed may be indicative of a process specification that is no longer appropriate. A review of the process may be needed. 评估环境监测工艺的可靠性时，得出的行动等级比当前等级更高时，可能说明此工艺规格不再适用。可能需要审核工艺。

b. Several consecutive points or drifts may be considered to be a pattern or cluster formation that, if above the alert level, signals a trend that requires an investigation. 连续几个点或漂移可能被认为是一种模式或集群的形成，如果超过警戒水平，标志着趋势需要进行调查。

c. Significant fluctuations or jumps in the values for the process are also significant where recurring cycles may point to seasonal variations. 工艺值的重大波动或跳跃同样重要，反复循环可能表明季节性变化。

d. One or more values markedly higher or lower than the majority of the data may or may not be process outliers. 一个或多个值明显高于或低于大多数数据可能是或不是工艺异常值。

Understanding the potential impact of the results generated during environmental monitoring is critical to a successful environmental monitoring program. 了解环境监测期间产生的结果的潜在影响对成功进行环境监测计划非常关键。

3.6 Characterization of Isolates 分离株识别

Characterizing microorganisms recovered from environmental and personnel monitoring is an important part of surveillance programs. The characterization system selected by the laboratory should be defined in writing, including the frequency of characterization and the standard procedures for the methods. 识别从环境和人员监测复原的微生物是监测计划的重要组成部分。实验室选择的识别系统应以书面形式确定，包括识别频率和方法的标准程序。

Initially, many isolates may be characterized to establish a database of the microorganisms found in the area. 最初，可能识别许多分离株，以在区域中建立一个微生物数据库。

Characterization may include any of the following examples: morphology, Gram stain, automated or manual identification systems. See Appendix B for additional information on identification systems. 识别可能包括以下例子：形态，革兰氏染色，自动或手动识别系统。其他信息见附录B的识别系统。

Not all isolates need to be speciated, but they should be characterized sufficiently to develop a database. Once a database is established, the number of isolates characterized may decrease, but routine characterization should continue to determine whether isolates are part of the normal microbial flora or represent something different. 不是所有的菌株必须生成物种，但他们应该具有足够的发展数据库。一旦建立了一个数据库，分离为特征的数量可能会降低，但应继续常规鉴定，以确定是否是分离的正常微生物菌群的一部分或代表不同的东西。

Characterization of isolates also may be useful in investigating situations such as positive sterility test results, positive media fill results, alert and action level excursions, or introduction of a common organism that may signal a developing resistance to a sanitizing agent. A change in the microbial flora or the introduction of a previously undetected species might signify a change in a system that should be investigated. Characterizations can be useful clues as to the possible source of isolates. For example, *Staphylococcus* species are commonly found on skin and the former *Pseudomonas* species are usually associated with water. (Many of these species have been re-classified, e.g., *Ralstoniapickettei, Buckholderia cepacia, Sterotrophomonas maltophilia.)* 分离株识别在调查情况下可能也很重要，如阳性无菌测试结果，阳性介质灌装结果，报警和行动等级偏离或可能表示对清洁剂产生抗药性的普通生物的引入。微生物菌落变化或以前未被发现物种的引入可能意味着一个应调查系统的变化。识别分离株的可能来源是有用的线索。例如，葡萄球菌种常见于皮肤，假单胞菌物种通常与水有关。 （其中许多物种已重新分类，例如，Ralstoniapickettei，*Buckholderia cepacia*，Sterotrophomonas *maltophilia*。）

The characterization of microorganisms is qualitative and relies on scientific training and good judgment. Microorganisms recovered from production environments may be highly stressed due to physical factors such as limited nutrients, contact with chemicals, or thermal stress. It may be difficult to obtain genus/species matches in identification system databases. The databases for commercial test kits and identification systems were designed originally for clinical isolates and may be incomplete with regard to industrial isolates; this may lead to misidentification of species or unidentifiable isolates. This area is continuing to be developed and enhanced. 微生物的识别是定性的，依据科学的培训和良好的判断力。从生产环境中复原的微生物可能由于物理因素而非常重要，如有限的营养物质，接触化学品，或热应力。可能很难获得与识别系统数据库相匹配的种类/物种。商业测试工具和识别系统数据库的设计最初是为临床分离株，工业分离株可能不完整；这可能会导致物种错误识别或无法识别的分离株。持续发展并加强此区域。

3.7 Investigations/Corrective Actions 调查/纠正行动

When excursions occur, there may be a drift from the baseline. An investigation is needed to determine what happened and what should be done to prevent a recurrence. Records should show that the excursions were recognized and appropriate follow-up occurred. 出现偏差时，表明从基线有漂移。需要进行调查，以确定发生了什么，应该怎么做以防止类似事件再度发生。记录应表明偏差已确认且将进行适当的后续行动。

The overall purpose of the investigative action is to establish, to the greatest degree possible, a cause-effect relationship between the observed level of environmental quality and causes for the excursions (i.e., sources of contamination). 调查行动的总体目标是最大程度地建立环境质量等级和偏差原因（即污染源）之间的因果关系。

To create consistency in the treatment of excursions, investigative and/or corrective action steps should be pre-specified in a written plan. A progression of investigative/corrective actions or responses may be used in which sequential or multiple excursions require greater consideration than single or widely separate excursions. Likewise, excursions that occur in areas which are critical to the manufacturing process may require a more rigorous investigation and corrective action than those occurring in areas that are judged less critical to the integrity of the manufacturing process. 为建立偏差处理的一致性，调查和/或纠正行动步骤应预先以书面计划规定。调查进展/纠正措施或反应可能用于一系列或多个偏差比单个或独立偏差需要更多考虑的地方。同样地，生产工艺关键区出现的偏差可能比工艺完整性次关键区需要更严格的调查和纠正措施。

When an alert/action level is exceeded, the following actions may be appropriate: 超过报警/行动等级时，以下行动可能适用：

• Notify the appropriate management.通知相关管理部门

-Initiate an investigation to determine the causes and consequences of the excursion from the specified operating parameters. 展开调查，以确定与指定操作参数漂移的原因和后果。

•Perform corrective actions to address the problem, as needed. (A table of typical corrective actions follows.) 根据需要执行纠正行动，以解决这一问题。 （一个典型的纠正措施表如下。）

•Follow-up review to assess effectiveness of corrective action. 后续审查，以评估纠正行动的有效性。

The previous listing is not all-inclusive, as these recommendations are only intended to suggest investigative activities and corrective actions when sampling and laboratory failures have been ruled out. Appropriate corrective actions are dependent upon the individual facility's design and process designs. 以前列表并非包括全部，因为当取样和实验室失败被排除后，这些意见只是建议调查活动并提出纠正措施时。适当的纠正行动取决于每个设施的设计和工艺设计。

The reviewer may exert scientific judgment to postpone any corrective action until the result is confirmed and/ or an investigation has been completed. It may also be appropriate to provide management with a routine summary of action level excursions for review. All corrective actions listed include an evaluation of the action for effect on the product. 审核者可能进行科学判断以推迟任何纠正措施，直至结果已确认和/或调查工作已经完成。也可提供行动等级偏差的日常总结用于审核。所有列出的纠正措施包括对产品影响的评估。

3.8 Documentation 记录

The following list includes items to be considered for documentation records: 以下包括文件记录需考虑的方面

a. Date and time of test 测试日期和时间
b. Test method/procedure reference 测试方法/程序参考
c. Activity level at site during test 测试过程中现场活动级别
d. Equipment identification 设备识别

e. Location 位置
f. Area classification 区域分级
g. Schematics of areas showing sample site locations 表明样品位置的区域示意图
h. Sample site (critical or non-critical) 样品位置（关键或非关键）
i. Test results 测试结果
j. Evaluator of results 结果评估员
k. Date results read 日期结果读数
l. Alert and/or action level 报警和/或行动等级
m. Temperature and duration of incubation 培养温度和持续时间
n. Control test results 控制测试结果

o. Certification date, validation date, and expiration date of media used 所用介质的认证日期，确认日期和失效日期

p. Characterization of contaminants 污染物特征

q. Name of reviewer 审核人姓名

r. Reporting of data 数据报告

s. Review of historical data 历史数据审核

t. Change control system 变更控制系统

u. Calibration date on instrumentation 仪器校验日期

v. Methodology, analysis used to specify action/alert levels 指定行动/报警等级使用的方法，分析

w. System for documenting investigative/corrective action: 记录调查/纠正行动的系统

(1) Description of deficiency 缺陷说明

(2) Possible cause(s) of problem 出现问题的可能原因

(3) Identification of persons responsible for relevant corrective action 负责有关纠正行动人员鉴定

(4) Description of action steps and their schedule for implementation 行动步骤说明和实施时间表

(5) Evaluation of effectiveness of action steps 行动步骤有效性评估

Typical corrective actions for different systems. 不同系统的典型纠正行动

• **Compressed Gas System** 压缩空气系统	• Repeat test immediately. 立即重复测试 • Integrity test the filter. 过滤器完整性测试 • Check and, if necessary, replace filter if excursion confirmed on retest. 检查，复检确认有偏离时，如必要，可置换过滤器 • Evaluate impact upon processed component and/or product. 评估对处理后组件和/或产品的影响。
• **Room Air/HVAC 室内空气/空调系统**	• Review level of personnel activity. 审核人员活动等级 • Review/perform air flow patterns/smoke tests. 审核/进行空气流型/烟雾测试 • Review aseptic technique of personnel. 审核人员的无菌技术 • Review gowning requirements for area. 审核区域更衣要求 • Inspect incoming air filters for leaks in filter and pressure differential across filter. 检查进气过滤器泄漏情况和过滤器压差。 • Review room disinfection/sanitization procedures, sanitization intervals, and disinfectant efficacy. 审核室内消毒/杀菌程序，消毒时间间隔和消毒效果。 • Check area pressure differentials, particularly with respect to the last sanitization. 检查区域压差，特别是最后杀菌。 • Evaluate mechanical equipment in area as possible source of contamination. 评估可能为污染源区域中的机械设备。 • Evaluate integrity of the room (e.g., peeling paint, cracks in ceiling, walls, and floor). 评价房间完整性（例如，油漆剥落，天花板，墙壁和地板裂缝）。 • Review risk to product. 审核产品风险
• **Facility Surfaces 设施表面**	• Perform investigation for possible sources of contamination. 进行潜在污染源调查 • Evaluate sanitization/disinfection practices review cleaning records. 评估杀菌/消毒规范，审核清洗记录

	• Review possible unusual events during manufacturing operation. 生产运行过程中审核可能发生的异常事件 • Examine areas during usage. 使用时检查区域 • Verify that controls were not circumvented. 确认进行控制 • Review risk of product contact. 审核产品接触的风险 • Determine sensitivity of isolate to disinfectants being used. 确定使用的分离株对消毒剂的敏感性。 • Review isolates for occurrence in other types of tests. 审查其他测试类型中的分离株。
• **High Purity Water Systems (WFI, clean steam, purified water)** **高纯水系统（WFI，洁净蒸汽，纯化水）**	• Examine endotoxin and water chemistry data for system. 检查系统内毒素和水的化学数据 • Examine bioburden data for other samples or sites in system -port contamination vs. system contamination. 检查系统端口污染vs.系统污染中其他样品或位置的生物负荷数据。 • Review efficacy of sanitization procedure and schedule. 审查消毒程序和时间表的效力。 • Inspect system preventive maintenance records. 检查系统预防性维护记录。 • Verify integrity of sample collection and use procedures. 确认样本收集和使用程序的完整性。 • Inspect system for dead-legs, proper sloping, proper sample port design and location. 检查系统死角，适当倾斜，适当样本端口设计和位置。 • Evaluate impact upon processed component and/or product. 评估对已处理部件和/或产品的影响
• **Personnel Gowning (gowning and gloves)** **人员更衣（更衣和手套）**	• Evaluate possible operator impact upon product. 评估操作员对产品的潜在影响 • Review sterility test data. 审核无菌测试数据 • Review other environmental monitoring data for area. 审核区域的其他环境监测数据 • Review preparation and expiry dates for disinfectants used on gloves. 审核手套上使用的消毒剂制备和有效期 • Identify all morphologically unique isolates (human vs. environmental). 确认所有形态独特的分离株（人员vs. 环境） • Evaluate training of operator. 评估操作者培训 • Interview operator for potential causes. 询问操作员潜在原因 • Retrain/requalify operator. 对操作员进行再培训/再确认

4.0 SYSTEM SURVEILLANCE 系统监视

4.1 Introduction 简介

4.1.1 Terminal Sterilization 最终灭菌

The terminal sterilization environmental control program is concerned with microbial flora that contributes to the bioburden and endotoxin content of the product prior to sterilization. This includes distilled water, sterilizer cooling water, treated water and city water. Air, surfaces, and microbial levels of containers and closures are also

routinely monitored. While control of the environment in which the products are prepared is important, the most critical aspect of the program is the bioburden of the filled product to be sterilized. Controlling this aspect of the manufacturing process ensures that the spore (heat resistant) bioburden levels presented to the product sterilization cycle do not exceed the validated capabilities of the process and that the desired sterility assurance levels are achieved. 最终灭菌的环境控制程序有关于灭菌前会导致产品生物负荷和内毒素含量的微生物区。这包括蒸馏水，灭菌器冷却水，经处理的水和城市供水。容器和密封系统的空气，表面和微生物等级仍定期监测。虽然制备产品的环境控制很重要，该程序最重要的方面是准备灭菌的已罐装产品的生物负荷。控制生产工艺的此方面是确保产品灭菌周期的孢子（耐热）生物负荷等级不超过工艺处理能力，且达到所需的无菌保证水平。

4.1.2 Aseptic Filling 无菌灌装

The aseptic environmental control program is specifically designed to determine the number and type of microorganisms associated with direct assembly or preparation of product prior to sealing of the filled containers. The number of sample sites and frequency of monitoring are generally greater than that monitored for established terminal sterilization processes. Air, water, personnel, compressed gases, floors, walls, machinery, and other surfaces within the filling room are routinely monitored. Adequate environmental control is an integral part of the aseptic manufacturing process and a critical factor in contributing to sterility assurance. A review of the routine environmental control data should be included in the manufacturing documentation for aseptically filled products. 无菌环境控制程序用于在密封已灌装容器前确定与直接组装或产品制备相关的微生物数量和类型。样品位置数量和监测频率通常比监测最终灭菌工艺的更大。定期监测灌装室的空气，水，人员，压缩气体，地板，墙壁，机械和其他表面。充分的环境控制是无菌生产工艺的必要组成部分，也是无菌保证的关键因素。常规环境控制数据的审查应列入无菌灌装产品的生产文件中。

4.1.3 Isolation Technology 隔离技术

The environmental control program for aseptic filling isolator systems may be similar to that used for a conventional aseptic filling operation with the exception of surface and personnel monitoring. After sufficient data is collected, routine surface and air monitoring may not be warranted if a validated sanitization cycle exists for the interior surfaces of the isolator. However, particulate air sampling might be performed routinely if the product might be adversely affected by higher than normal environmental particulate levels. Surface monitoring may be used during initial validation runs to support the effectiveness of the sanitization cycle and maintenance of clean isolator surfaces between sanitization cycles. If surface monitoring is performed, it should be done after the completion of filling so as to not introduce any extraneous contamination or residual growth media during the filling operation. Monitoring of personnel is not required for isolator systems, however, monitoring of isolator gloves/half-suits should be considered. 无菌灌装隔离器系统的环境控制程序除了表面和人员监测外，可能类似于传统无菌灌装操作程序。收集到足够数据后，如果隔离器内表面存在经验证的杀菌周期，可能不会确保进行日常表面和空气监测。然而，如果产品受到高于正常环境微粒等级的不利影响后，可能会定期进行空气微粒取样。初步验证可能使用表面监测以支持杀菌周期及此周期期间的隔离器洁净表面维护的有效性。如进行表面监测，需在灌装完成后进行，以防在灌装过程中引入外部污染或导致残余介质的增长。隔离器系统不需要人员监测，但是，隔离器手套/半更衣应予以考虑。

4.2 Water Monitoring 水监测

Water is a widely used substance, raw material, or ingredient in the production, processing, and formulation of many pharmaceutical products. Control of the

microbial quality of water is of great importance in the pharmaceutical manufacturing facility since it may be used for formulating product, as well as for various washing and rinsing processes. Once a water system is validated and shown to be in a state of control, appropriate samples should be taken from the holding and distribution system to assess the microbiological quality of the water for its intended use. As pointed out in other sections of this report, there are many considerations in establishing an appropriate site for sampling (e.g., facility design, line configurations, validation data, process, historical data, test methodology, etc.). For additional information, see the Appendix C. 水是一种广泛使用的产品物质，原料或配料，用于许多药品的加工和配方。对水的微生物质量控制对制药生产设施至关重要，因为它可用于制备产品，也用于各种清洗和冲洗过程。水系统进行验证，并证明处于控制状态时，应从维持和分配系统获取适当样品，以评估水中的微生物质量是否符合预定用途。正如本报告的其他章节所述，建立取样的适当位置有诸多考虑（例如，设施的设计，线路配置，验证数据，工艺，历史数据，测试方法等）。其他信息请参阅附录C

In the United States, the source or feed water should meet the requirements of the National Primary Drinking Water Regulations (NPDWR) (40 CFR 141) issued by the Environmental Protection Agency (EPA). There is a corresponding EU drinking water standard. These requirements ensure the absence of coliforms. 在美国，供给水源应符合环境保护局（EPA）发布的国家主要饮用水条例（NPDWR）（40 CFR141）的要求。有相应的欧盟饮用水标准。这些规定确保不存在大肠菌群。

Note: the plate count methodologies described below were obtained from the Standard Methods for the Examination of Water and Wastewater, 19th edition. 注：下述平板计数法根据水和废水的标准方法获得，第19版。

It is recognized, however, that other combinations of media, time, and temperature of incubation can be appropriate. Recommended methodologies from "Water for Pharmaceutical Purposes" general information chapter <1231> of USP 24 are described below. 然而培养的介质，时间和温度的其他结合可能也适用。美国药典24中"制药用水"总说明信息"1231"推荐的方法如下。

Drinking Water (City Water and Potable Water) 饮用水（城市用水和自来水）

Residual chlorine in the potable water needs to be neutralized with sodium thiosulfate. 饮用水中余氯需与硫代硫酸钠中和。

Sampling - Collect samples in a manner consistent with manufacturing practices. For example, if use points are routinely flushed prior to use, it is appropriate for samples to be collected with the same flush cycle. On the other hand, if use points are not normally flushed, there should be no flush prior to sample collection. It is also recommended to sample through hoses and not directly from the tap if manufacturing practices require the use of hoses. Do not sample from leaking taps (leaking taps should be repaired prior to use for processing and testing). Carefully choose distribution system sample locations to demonstrate microbiological quality throughout the distribution system. Start microbiological examination of water promptly after collection. If immediate processing is not possible, refrigerate samples at 2° - 8°C upon receipt in the laboratory. Time elapsing between collection and examination generally should not exceed 24 hours. 取样-按照生产规范收集样品。例如，如果使用点在使用前进行冲洗，样品应通过相同的冲洗周期收集。另一方面，如果使用点未正常冲洗，样品收集前不需冲洗。如果生产规范要求使用软管，建议从软管处进行取样，而不是直接从水龙头收集。不要从漏水的水龙头取样（生产和测试前漏水的水龙头应修理好）。仔细选择分配系统取样位置，以整个

分配系统的微生物质量。收集后立即进行水的微生物检验。如果不能立即处理，接收后将样品冷藏于实验室2° - 8°C温度下。收集和检查之间的时间一般不超过24小时。

Similarly, purified water and water for injection systems should be monitored at sufficient points and with sufficient frequency to ensure appropriate microbiological quality is maintained throughout the system and at all points of use. 同样，应在足够的位置以足够的频率监测纯净水和注射用水系统，以确保整个系统和所有使用点的微生物质量适合。

4.3 Compressed Gas Monitoring 压缩气体监测

The use of compressed air and compressed gas in aseptic environments may adversely affect the environmental conditions if appropriate precautions, routine testing and critical controls are not designed into the system. The following points should be considered: 如果系统无适当的预防措施，常规检查和关键控制，无菌环境下使用压缩空气和压缩气体可能会对环境条件产生不利影响。需考虑以下几点：

- Compressed gases used to pressurize or blanket product in sterile holding tanks should be introduced via hydrophobic vent filters and monitored at a frequency that assures that the gas does not challenge the bacterial retention of the filter. 对无菌储存罐中产品进行加压或覆盖的压缩气体应通过疏水排气过滤器通入，并以确保气体不挑战过滤器细菌截留的频率进行监测。
- Compressed air/gas that is used in aseptic environments should be filtered through sterilizing-grade filters and tested on a frequency that assures that the air/gas does not adversely effect the environment. 无菌环境中使用的压缩空气/气体应通过无菌级过滤器进行过滤，并以确保空气/气体不对环境产生不利影响的频率进行测试。
- All compressed air connections which do not affect the air to the workspace should be monitored with less frequency, however, any connection which introduces air to the environment should be monitored on a frequency as to assure the conditions of the environment class. 所有不影响工作区的空气的压缩空气连接应低频监测，但是，任何将空气引入环境的连接应以确保环境等级的频率进行监测。
- A medium used for evaluation and incubation and rendering evaluations should follow the standard practice as is done for normal monitoring sites. 用于评价，培养和和展现评价的介质应遵循正常监测点使用的标准规范。

4.4 Air Monitoring 空气监测

A comprehensive environmental monitoring program should include routine monitoring of both viable and non-viable airborne particulates. Viable particulates are generally of most concern in sterile product manufacturing environments; however, non-viable particulates should also be monitored as a reliable indicator of the proper function of the environmental control systems. Viable bacteria derived from people are typically associated with skin flakes, so higher non-viable particulate counts may be indicative of increased viable counts. Current techniques for monitoring viable particulates in air are limited by: (a) the equipment available, (b) the time necessary to demonstrate the presence of microorganisms in the sample of air taken, (c) the inability to re-sample the environment in a timely fashion when results warrant, and (d) difficulties in continuously monitoring the environment due to considerations such as drying out of the culture media. 一个全面的环境监测计划应当包括活性和非活性空气微粒的常规监测。活性微粒通常是无菌产品生产环境最关注的，但是，非活性微粒也应作为环境控制系统功能的一项可靠指标进行监测。来自人的活性细菌通常与皮屑有关，所以更高的非活性粒子数可能表明增加的活性粒子数。监测空气中活性微粒的现有技术受以下限

制：（a）现有设备，（b）证明所取空气样本中存在微生物的所需时间，（c）未能及时对环境进行再取样和（d）连续监测环境的难度，如培养介质干燥等。

Although the use of high efficiency particulate air (HEPA) filters to remove particles from the air is a very effective way to reduce the particle load in an environment, especially under static conditions, normal activity levels of equipment and people in a room may greatly reduce their effectiveness. People are a major contributor of viable and non-viable particulates to the environment. The intent of an airborne environmental monitoring program is to determine if there are viable and/ or non-viable airborne particulates in locations that would allow them to settle on product contact surfaces and thereby find their way into process intermediates or final product. FDA expects monitoring under dynamic conditions (1), however outside of the United States, static monitoring may be necessary in addition to dynamic monitoring to satisfy regulatory requirements. 虽然使用高效空气过滤器（HEPA）去除空气中的粒子是减少环境中微粒负荷的一种非常有效的方法，尤其在静态条件下，但设备和人员的正常活动水平可能会大大降低其有效性。人员是对环境产生活性和非活性微粒的重要因素。空气环境监测计划的目的是确定在粒子可能沉降的产品接触表面，即可寻找到工艺中间体或最终产品途径的位置是否有活性和/或非活性空气粒子。 FDA希望在动态条件（1）下监测，但对美国以外的区域，为满足法规要求，除了动态监测外可能也需要进行静态监测。

For most older-model samplers, the sampling volume is less than one cubic meter. A sampling volume of ten cubic feet is considered insufficient in Europe. Many of the newer model samplers are also capable of sampling one cubic meter. 对于大多数旧型采样器，取样量不足1立方米。在欧洲，十立方英尺的取样量被认为是不足的。许多较新的采样器可对一立方米进行取样。

4.4.1 Non-Viable Monitoring 非活性微粒监测

Monitoring of non-viable airborne particulates is a necessary component of an environmental monitoring program. Such monitoring demonstrates control of potential contaminants in the environment to which the product, during the manufacturing process, is exposed. Classification of production areas is generally made based upon the level of non-viable particulates in the air. 非活性空气微粒监测是环境监测计划的必要组成部分。这种监测表明对生产过程中产品暴露环境中潜在污染物的控制。一般根据空气中非活性微粒等级进行生产区分级。

Federal Standard 209E describes, in detail, classification of air cleanliness for clean-rooms and clean zones based on specified concentrations of airborne particulates. It prescribes methods for verifying air cleanliness in the traditional particulate size range(s) and also with respect to ultra-fine particles. This document has been commonly referenced with respect to non-viable particulate monitoring in the pharmaceutical, biological, biotechnology, and medical device industries as well as the electronics industry. More recent publications on the classification of air cleanliness are the ISO 14644 series of standards on "Clean rooms and associated controlled environments," and ISO 14698 series of standards on "Biocontamination in a clean room environment." Following the publication of the ISO 14644-1 and 14644-2 standards, Federal Standard 209E is expected to be retired (as a standard for conducting business with the US government) by the end of 2001. 联邦标准209E根据空气微粒的规定浓度详细介绍了洁净室和洁净区空气洁净度的分级。它规定在传统微粒及超细微粒大小范围内确认空气洁净度的方法。本文件经常用于制药，生物，生物技术，医疗设备行业以及电子行业的非活性微粒监测。空气洁净度分级的最近出版物为ISO 14644标准系列的"清洁室和相关受控环境"和ISO 14698标准系列的"洁净室环境的生物污染"。ISO 14644-1和14644-2标准出版后，联邦标准209E预计将在2001年年底停止使用（与美国政府做生意的标准）。

The 1987 FDA aseptic processing guide recommends daily monitoring for non-viables during operations, and in the United States, monitoring non-viable particles equal to or larger than 0.5μm during routine manufacturing operations is common (exceptions include aseptic powder filling operations). Although monitoring particles in different size ranges may seem prudent, particles of 0.5 μm and larger are generally recognized as indicators of environmental contamination. Requirements outside of the United States may also include monitoring 5.0μm particles. 1987年FDA的无菌工艺指南建议在运行过程中进行非活性微粒的日常监控，在美国，日常生产正常运行时监测等于或大于0.5μm的非活性粒子（例外包括无菌粉灌装操作）。虽然监测不同尺寸范围的粒子可能需谨慎，0.5μm及更大的颗粒通常认为是环境污染的指示器。美国以外的需求可能还包括监测5.0μm粒子。

A commonly used monitoring method is optical particle counting. It is based on the principle of passing an aerosol through a focused light source, which results in light scattering from single particles by refraction, reflection, and diffraction. In this way, both the size, based on the intensity of the scattered light, and the number of particles can be measured simultaneously. This method provides real-time data on the environment and provides a useful tool to demonstrate that the environment remains in a state of control with respect to particulate contamination. 常用的监测方法是光粒子计数。根据气溶胶穿过集中光源，从单个微粒折射，反射和衍射散射光的原理。这样，根据散射光强度可同时测量和粒子尺寸和数目。此方法提供环境的实时数据，并为证明环境中微粒污染仍处于控制状态提供一个有用的工具。

Selection of an optical particle counter for use in a clean room or other controlled environment is typically based on such factors as sensitivity, flow rate, particle size range, portability, data storage capability, alarm capability, construction, and sanitization compatibilities. Although there are technical differences between instruments from different manufacturers, it is generally accepted that these instruments are interchangeable. However, when switching from one manufacturer's instrument to another's, it may be prudent to assess whether a change in alert or action levels is indicated, due to differences in equipment sensitivity. 洁净室或其他受控环境中光粒子计数器的选择通常根据灵敏度，流速，颗粒大小范围，便携性，数据存储功能，报警功能，建设和卫生处理相容性等因素。虽然不同供应商的仪器之间存在技术差异，通常认为这些工具是可以互换的。然而，当从一个制造商的仪器切换到另一个时，由于设备灵敏度的差异，可能需审慎评估是否指示警戒或行动等级。

In addition to portable particle counters, systems have been developed for permanent installation in manufacturing areas to allow continuous monitoring of the manufacturing process with centralized data storage and alarm capabilities. 除了便携式颗粒计数器，系统适用于生产区的永久性安装，以允许持续监测带集中数据存储和报警功能的生产工艺。

4.4.2 Viable Monitoring 活性微粒监测

Microbes in air are generally associated with solid or liquid particles. These particles may consist of a single unattached cell or more commonly as clumps of organisms. Organisms may adhere to a dust particle or other "raft," or, if unattached, exist as a free-floating particle suspended in the air. These particles may remain suspended in the air for extended periods of time due to the local air currents. HVAC systems in controlled environments are designed to remove these particles through frequent air changes or with unidirectional airflow in critical areas. 空气中微生物一般为固体或液体颗粒。这些粒子可能由单一的非附着细胞或更常用的有机物团块构成。有机物可能附着在尘埃粒子或其

他"漂浮物"上，如果非附着，则作为一个自由的颗粒悬浮在空气中。由于当地气流，这些粒子可能长时间悬浮在空气中。控制环境中的空调系统的设计旨在通过频繁空气变更除去这些颗粒或关键区的单向气流。

Although total particulate determinations can be useful in monitoring air quality in a pharmaceutical, biotech, biological, or medical device facility, viable airborne contamination is of primary importance in manufacturing environments that require control of bioburden in the final product. This is particularly true for aseptic production processes, although it applies to all production processes requiring control of viable contaminants in the final product (including those used to manufacture terminally sterilized products). 虽然总微粒测定可用于制药，生物技术，生物或医疗设备设施的监测，生产环境中的活性空气污染非常重要，要求控制最终产品的生物负荷。无菌生产过程尤其如此，虽然适用于所有要求控制最终产品活性污染物的生产工艺（包括用于生产最终灭菌产品的工艺）。

4.4.2.1 Sites 位置

The principles previously mentioned for site selection in Section 3.2 are applicable. However, in addition to these general considerations for sampling site selection, there are considerations more specifically aimed at airborne monitoring. A monitoring location specified for critical areas (i.e., Class 100, laminar flow) by the 1987 FDA *Guideline on Sterile Drug Products Produced by Aseptic Processing* is not more than one foot away from the work site, and upstream of the air flow, during filling/closing operations. It is important to consider air flow patterns in choosing these critical sampling locations, as well as the introduction of potential contaminants by environmental monitoring personnel, equipment, and practices. The potential for contamination of the product due to the necessity of monitoring must be considered and avoided. 3.2节中先前提到的位置选择原则适用。然而，除了取样位置选择的一般性的考虑，空气监测还有其他具体的考虑。灌装/密封操作过程中，1987年FDA无菌加工生产的无菌药品指南指定关键区（即100级，层流）的监测位置距离工地，气流上游不应超过一英尺。选择这些关键取样地点需考虑空气流型以及环境监测人员，设备和行动可能引入潜在污染物。必须考虑并避免由于监测导致的产品潜在污染。

Additional monitoring locations should be chosen based upon a defined rationale for the remainder of the room in which the process is occurring. This can be based upon initial validation/qualification sampling of the environment, personnel flow, and processing activity levels. 其他监测位置应根据工艺房间残余物的规定原则进行选择。这可能基于环境，人流和生产活动等级取样的初步验证/确认。

4.4.2.2 Methods 方法

The FDA currently expects active air sampling of environments on a routine basis to demonstrate control of possible viable airborne particulates (see reference, Section 4.4). Therefore, although useful in some circumstances, passive methods such as settling plates are not generally recommended for such monitoring programs in the United States. Generally, quantitative sampling methods are required, with operating levels being defined per unit volume of air. FDA目前要求对环境空气进行常规的主动采样，以证明控制可能存在的活性空气微粒（见参考资料，第4.4节）。因此，尽管在某些情况下有效，美国的监测程序中通常不推荐被动方法，如沉降板。通常要求采用定量取样法，操作等级按照每单位的空气量定义。

Presently, several countries outside the United States require the use of settling plates as well as active air sampling. Thus, an airborne monitoring program may require the use of both active and passive air sampling methods to satisfy the

requirements of the countries in which the final product will be sold. Settling plates may also be useful for monitoring isolators or laminar airflow cabinets. 目前，美国以外的一些国家要求使用沉降板以及主动空气采样。因此，空气监测程序可能需要使用主动和被动空气取样法，以满足最终产品销往国家的要求。沉降板也可用于监测隔离器或层流柜。

4.4.2.3 Equipment 设备

A number of types of viable airborne sampling devices are currently used routinely in the industry, and others are available for particular uses such as viable particle size distribution. The most commonly used types of equipment will be presented here to attempt to provide an overview of the advantages and disadvantages associated with each instrument. These considerations are, of course, subject to individual interpretation, specialized uses, and application to traditional clean rooms or to barrier/isolation systems. 活性空气取样装置的几种类型目前用于工业，其他用于特定用途，如活性微粒大小分布。设备最常用的类型将在此处列出，以提供每个仪器相关优点和缺点的概述。当然这些考虑取决于个人解释，专门用途，传统洁净室或屏障/隔离系统的应用。

Generally, active air samplers are used for monitoring viable airborne contamination levels in production facilities. These instruments allow the measurement of known volumes of air, allowing quantification of airborne viable contaminants by unit volume of air. 通常主动空气采样器用于监测生产设施的活性空气污染程度。这些仪器允许测量已知的空气量，允许量化单位空气量中的空气活性污染物。

The most widely used instruments are of the solid culture medium impaction type. These include the following categories and representative instruments: 最广泛使用的仪器为固体培养基碰撞型。这些包括以下类别和代表性仪器：

1) Slit Impactors 狭缝碰撞器

Slit-to-Agar (STA) Air Sampler 狭缝对琼脂（STA）空气采样器

The slit-to-agar air sampler utilizes a revolving agar plate at a precise distance from a slit-type orifice to impinge the air sample (and particles) directly onto the surface of a solid nutrient collection medium. 狭缝对琼脂空气采样器在距离狭缝型孔板一定的距离，用旋转琼脂板将空气样品（及微粒）直接碰撞到固体培养基表面。

Advantages: 优点

- Measures a large volume of air 测量空气量大
- Time-concentration relationship is available 存在时间-浓度关系
- Remote sampling probe can be used 可使用远程取样探头
- Can be used for sampling compressed gases 可用于压缩气体取样

Disadvantages:缺点

- Equipment is large and cumbersome 设备大，笨重
- Some equipment cannot be steam sterilized 一些设备不能蒸汽灭菌
- Some systems require 150 mm agar plates 一些系统要求150mm的琼脂板

2) Sieve Impactors 筛子碰撞器

Surface Air Sampler 表面空气采样器

The SAS air samplers operate on the principle that air is drawn into the unit by means of an impeller, is drawn over the surface of a contact plate, and is exhausted. SAS空气采样器操作原理是空气通过叶轮导入设备，覆盖在接触板表面并耗尽。

Advantages: 优点

- Convenience 方便
- Speed 速度
- Portability and flexibility 便携性和灵活性
- Self-contained power supply 自带电源
- Perforated cover plate can be steam sterilized 冲孔盖板可采用蒸汽消毒
- Measures a large volume of air 测量大量空气
- Uses standard contact plates 使用标准接触板
- Airflow can be calibrated 流速可校验

Disadvantage: 缺点

- Equipment is somewhat cumbersome 设备有点笨重

Surface Vacuum Sampler 表面真空采样器

This sampler utilizes a simple stainless steel chamber containing a Petri dish filled with nutrient collection medium. An air sample (and particles) is drawn across the surface of the plate using a vacuum source, thereby depositing the particles onto the surface of the solid medium. A centrally installed system and a portable system are also available. 这种采样器采用简单的不锈钢腔体，腔体包含带营养收集介质的有盖培养皿。空气样品（和颗粒）用真空源穿过板表面，从而将颗粒沉积到固体培养基表面。中央安装系统和便携式系统也可提供。

Advantages: 优点

- Small size allows relatively easy placement along filling lines and in small areas and enclosures 体积小可以比较容易置于灌装线，小区域和密封系统
- Entire sampling unit can be steam sterilized 整个取样设备可进行蒸汽灭菌
- Can be used for sampling compressed gases 可对压缩气体进行取样
- Can be remotely placed in small isolators 可远程放置在小隔离器中
- Airflow can be calibrated 流速可校验
- Able to sample large volume of air 可对大量空气进行取样

Disadvantage: 缺点

- Equipment is somewhat cumbersome (with vacuum source) 设备有点笨重（带真空源）

3)Centrifugal Impactors 离心碰撞器

Centrifugal Samplers 离心采样器

These air samplers operate on the principle that air is drawn into the unit by means of an impeller and the particles are deposited on the surface of a solid nutrient collection medium (strip) by centrifugal force. 这些空气采样器操作原理是空气通过叶轮导入设备，颗粒通过离心力沉淀在固体营养收集介质表面。

Advantages: 优点

- Convenience 方便
- Speed 速度
- Portability and flexibility 便携性和灵活性
- Self-contained power supply 自带电源
- Head assembly can be steam sterilized 磁头组件可蒸汽灭菌
- Measures a large volume of air 可测量大量空气
- Airflow can be calibrated 流速可校验

Disadvantages: 缺点

- Single source for media strips 介质指示剂来源单一
- Direct calibration of sampling volume not possible 不可能校验取样量

- Laboratory handling of media strips is a typical (i.e., requires more handling inserting and removing the strip into the head) 介质指示剂的实验室处理是典型的（即需要更多的处理插入并将指示剂移到端部）
- Potential disruption of laminar airflow by turbulent input and exhaust air 湍流输入和排气会对层流产生潜在干扰

4)Filtration 过滤

This method uses an air sampler which employs a vacuum source to draw air through a filter where particles are collected on the filter. The filter is aseptically removed for culturing in the laboratory on an appropriate nutrient medium. 此方法使用空气采样器，真空源将空气穿过过滤器，颗粒收集到过滤器上。无菌移去过滤器，在实验室适当的营养培养基上进行培养。

Advantages: 优点

- Measures a large volume of air 测量空气量大
- Wide choice of filter media and pore sizes available 过滤介质和孔径选择范围广
- Use of gelatin membrane filters may be useful to overcome desiccation of collected microorganisms 明胶膜过滤器的使用可能有助于解决已收集微生物的脱水问题
- Filter holder is sterilizeable 过滤器支撑可灭菌
- Airflow can be calibrated 流速可校验
- Usable in isolators 隔离器中可用

Disadvantages: 缺点

- Membranes with collected samples must be placed on nutrient media for enumeration of viable microorganisms 含已收集样品的膜必须置于营养介质中，以统计活性微生物数
- Equipment is somewhat cumbersome 设备有点笨重

5) Liquid Impingement 液体碰撞

In this method, air is delivered through a tube whose outlet is submerged beneath a liquid collection medium. Viable particles are impacted into the liquid medium

while the gas phase rises and is removed from the system. 在此方法中，空气通过管道传递，其出口浸于液体收集介质中。活性粒子影响到液体培养基，气相上升并从系统中移除。

Advantages: 优点

- Allows samples with high viable counts since liquids can be diluted before sampling 允许高活性数的样品，因为液体在取样前可以稀释
- Allows choice of collecting medium such as Phosphate Buffered Saline (PBS) or media (media may require anti-foaming agent) 允许收集介质，例如磷酸盐缓冲液（PBS）或介质（介质可能需要抗泡剂）
- Measures vegetative cells and spores 测量营养细胞和孢子
- Vegetative cells are more apt to survive in the liquid media 营养细胞在液体介质中更易存活
- Inexpensive 便宜

Disadvantages:缺点

- High velocity impingement could destroy vegetative cells 高速撞击可能会破坏植物细胞
- Sample handling may cause contamination 样品处理可能造成污染
- Breakable glass components 易碎的玻璃成分

6) Settling Plates or Liquid Media 沉降板/液体介质

This method involves the use of settling or fallout plates. There is a minimum and maximum time for use that must be determined/qualified. This method of air sampling utilizes a simple system of solid nutrient collection medium in a Petri dish, which is directly exposed to environmental conditions. Particles in the air settle out on the agar surface where they can be counted directly, after incubation. In general, settling plates are used in conjunction with active (volumetric) air sampling to yield a broader picture of the environment. 这种方法涉及到沉降板或漂浮物收集板的使用。此空气取样法在有盖培养皿中采用固体营养收集介质的简单系统，其直接暴露于环境条件。培养后，空气中的颗粒沉降在琼脂表面，可直接计数。一般来说，沉降板与活性空气取样一同使用，以产生更广泛的环境图。

In the settle bottle, a liquid medium is used rather than an agar, which minimizes desiccation during extended sampling times. With the advent of isolation technology, the use of settling plates and bottles are becoming more prevalent due to their smaller size. 沉降瓶中使用液体介质而不是琼脂，以最大限度地减少在延长采样时间内的脱水。随着隔离技术的出现，沉降板和沉降瓶由于尺寸更小，其使用也越来越普遍。

Advantages: 优点

- Ease of use 便于使用
- Economical 经济
- Virtually any media can be used 几乎任何介质都可以使用
- Small size allows relatively easy placement along filling lines and in small areas and enclosures such as biosafety hoods 体积小，可以比较容易安置在灌装线沿线，小区域和密封系统，如生物安全罩
- Allows "continuous" monitoring over prolonged periods of time by changing plates 通过换板来允许长时间"连续"监测
- No power connection required 无电源连接要求

- Settle bottles are essentially impervious to poisoning by sterilizing gases used in isolators沉降瓶基本上不受隔离器中灭菌气体污染

Disadvantages:

- Generally considered semi-quantitative at best for settle plates, (+) or (-) for settle bottles通常认为沉降板（+）或（-）沉降瓶的半定量为最佳
- Microbial count cannot be correlated with air volume 微生物数量不能与风量有关
- Particle deposition is affected by the size of the particles, temperature, and flow/volume of air passing across its surface 粒子沉积受粒子大小，温度和表面流量/空气量的影响
- Plates can desiccate if left exposed for too long a period 沉降板如长时间暴露，则会脱水

4.4.3 Surface Monitoring 表面监测

4.4.3.1 Introduction 简介

In addition to conducting viable air monitoring to determine the microbial bioburden surrounding the manufacturing operations, surface monitoring is conducted to determine the microbial bioburden of surfaces within the manufacturing area as well as on equipment and product contact surfaces. 除了进行活性空气监测，以确定生产操作周围的微生物负荷，进行表面监测以生产区表面，设备表面和产品接触面的微生物负荷。

4.4.3.2 Methodology/Test Method 方法/测试方法

The method of testing should be considered when the sampling plan is established. Care should be taken to consider the limitation in accuracy and reproducibility when choosing a method; influential factors include suitability for the surface type, criticality of the surface, and the type of information provided. The type of media used will influence the detection of representative flora from the sample site. Neutralizers may be added in the media to inactivate surfaces treated with chemical disinfectants. 建立取样计划时，应考虑测试方法。选择方法时，应考虑精确性和可重复性的限制；影响因素，包括表面类型的适用性，表面关键性和提供的信息类型。使用的介质类型将影响取样位置的代表性微生物群的检测。可以增加中和剂以对化学消毒剂处理的表面进行灭活。

The basic methods include contact plates, swabs and surface rinses. Each provides data that can be used to determine the impact (if any) on product quality. Testing methods can provide qualitative or quantitative information. Also, the accuracy of the sampling is impacted by the collection and handling of samples so proper training is essential to an effective sampling and testing program. 基本方法包括接触板，拭子和表面冲洗。每个提供可用于确定对产品质量影响（如有）的数据。测试方法可以提供定性或定量的信息。此外，取样精度受样品收集和处理影响，因此，适当的培训对有效的取样和测试程序是必不可少的。

4.4.3.2.1 Contact Plates 接触面板

Contact plates are commonly used because they are easy to use and they provide quantitative results. The plates are typically 50mm in diameter and are filled so that the media forms a dome. The media may contain a neutralizing agent, depending upon its intended use. The surface of the media is pressed against a flat surface,

resulting in a sampled area of approximately 25 cm^2. The sample plate is then placed in the incubator for the required period of time. Colonies, if present, are counted at the end of the incubation. Some of the disadvantages of this method are: (a) it is not suitable for irregular surfaces, (b) if the media is wet, microorganism confluence can occur, and (c) media residue must be removed from the sample site. 通常使用接触板，因为它们易于使用，且能提供定量结果。该板通常直径为50mm，填充介质形成一个圆形。介质可能包含中和剂，取决于它的用途。介质表面压在一个平面上，取样区域大概为25 cm2。取样板在规定时间内放置在培养皿中。若存在菌落，培养结束时进行计数。采用这种方法的缺点有：（1）它不适用于不规则表面，（二）如果介质是湿的，可能导致微生物合流，以及（c）介质残留必须从取样位置除去。

4.4.3.2.2 Flexible Films 柔性薄膜

Media can be deposited on a flexible substrate which can be used in an identical manner to that employed for contact plates. These films can also provide a defined sampling area. The surface of the media is pressed against a flat surface. The exposed film is then placed in the incubator for the required period of time. Colonies, if present, are counted at the end of the incubation. Some of the disadvantages of this method are: (a) it is not suitable for irregular surfaces, (b) if media is wet, microorganism confluence can occur, and (c) media residue must be removed from the sample site. 介质可以存放在一个柔性培养基上，与接触板的使用方式相同。这些薄膜也可以提供规定的取样区域。介质表面压在一个平面上。暴露的薄膜在规定时间内放置在培养皿中。若存在菌落，培养结束时进行计数。采用这种方法的缺点有：（1）它不适用于不规则表面，（二）如果介质是湿的，可能导致微生物合流，以及（c）介质残留必须从取样位置除去。

4.4.3.2.3 Swabs 拭子

This method is employed for equipment and irregular surfaces for which contact plates are not suitable. This method can be used on flat surfaces, provided a template is used to define the sample size - usually approximately 2 inches x 2 inches (approximately 25 cm^2). 此方法适用于接触板不适用的设备和不规则表面。这种方法可用于平面，只要有模板定义样本大小 - 通常大约2英寸×2英寸（约25平方厘米）。

Types of swabs that can be used for this method include cotton, Dacron™, and calcium alginate materials with the appropriate diluent. The cotton and Dacron™ swabs can be used to provide qualitative results by placing the used swab into broth media. They also can be used quantitatively and allow for diluting highly contaminated samples. Calcium alginate swabs, used with transport media, allow for the dissolving of the swab fiber, thus releasing the organisms into the solution for plating. Quantitative samples can be tested by the pour plate or membrane filtration method. Some disadvantages to this method are: (a) technique and sampling can affect results, and (b) requires manipulation to culture the sample. 此方法可使用的拭子包括棉花，涤纶™以及含稀释剂的藻酸钠材料。棉花与涤纶™拭子可通过将使用过的拭子放入肉汤介质以得到定性结果。他们还可以定量使用，并允许稀释高度污染的样品。藻酸钙拭子与传输介质一起使用可允许溶解拭子纤维，从而将有机物释放到电镀溶液。定量样品可通过倒板或膜过滤法进行测试。这种方法的缺点是：（a）技术和取样会影响结果，和（b）培养样品要求进行操控。

4.4.3.2.4 Surface Rinse Method 表面冲洗方法

This method is best used for large surface areas where the interior surface bioburden needs to be determined. This includes kettles, equipment trains, and tanks. Sterile

water is typically the fluid that comes in contact with the interior surfaces; it is then collected and tested by membrane filtration to yield a quantitative result. Some disadvantages are: (a) it is not suitable for many applications, (b) it requires extensive manipulations, and (c) techniques and sample processing can affect results. 这种方法最适用于需确定内表面生物负荷的大面积区域。这包括容器，设备机组和罐。无菌水通常是液体，与内表面接触；用膜过滤器进行收集和测试，以产生一个定量结果。一些缺点：（1）不适用于许多应用程序，（二）需要大量操作，以及（c）技术和样品处理可能影响结果。

Surface monitoring is a critical part of a viable environmental monitoring program that is employed to ensure the effective control of the aseptic processing area. The design of the program requires knowledge of the process in order to provide a meaningful sampling plan. 表面监测是活性环境监测程序的关键部分，用于确保无菌处理区的有效控制。该计划的设计需要工艺知识，以提供一个有意义的取样计划。

4.5 Personnel Monitoring 人员监测

4.5.1 Description 说明

Personnel are a primary source of contamination in an aseptic environment. It is therefore essential that all employees entering an aseptic environment be carefully selected and adequately trained so they can perform their required tasks in a well-disciplined manner. This training should include personal hygiene, an introduction to microbiology, aseptic techniques, and gowning. After an individual has been trained, routine microbiological monitoring of garments and finger impressions should be completed to assess the ongoing practice of aseptic technique. 在无菌环境中，工作人员是主要污染源。因此，若想高效地完成所要求的任务，就必须在进入无菌环境前对工作人员进行仔细的筛选并进行培训。培训应包括个人卫生、微生物学、无菌技术以及更衣。个人培训结束后，应完成工作人员服装和指纹的常规微生物监测，以评估无菌技术的实施。

4.5.2 Training/Certification of Personnel for Aseptic Manufacturing Area 无菌生产区人员培训/证书

Training/certification of aseptic area personnel may include but is not limited to, the following subject areas: 无菌区人员培训/证书可包含下列主题（但不限于此）：

a. Personal hygiene/habits 个人卫生/习惯

- Cleanliness of hair, skin, fingernails, and clothing 保持头发、皮肤、指甲、服装的干净整洁
- No make-up, nail polish, sculptured fingernails, glue-on nails, gum, candy 不化妆、不涂指甲油、不做指甲、不嚼口香糖、不吃糖
- No eating, drinking, chewing, or smoking 不吃东西、不喝饮料、不咀嚼、不吸烟

b. Illness 疾病

- Report all colds, flu, infections, wounds, or sunburn 报告一切感冒、流感、感染、创伤或灼伤
- Report all disease or chronic skin conditions 报告所有疾病或慢性皮肤病情况

c. Clothing 服装

- Dedicated plant or area uniforms required 工厂或区域的专用制服
- No watches or protruding jewelry 不佩戴手表及显露在外的首饰
- Protective clothing required 要求的防护服

d. Introduction to microbiology 微生物学的介绍

- Common sources of microorganism types 微生物种类的常见来源

*e. Introduction to aseptic techniques*无菌技术介绍

*f. Gowning practices*着装规范

- Personnel are documented to properly gown (i.e., not add contamination) via gowning certification. 人员需穿经认证的适当服装（即不会加大污染）
- Gowning certification may include additional sampling sites beyond those routinely monitored - the forehead, mask, neck area, back of head, garment zipper, arms, fingers. 除了那些常规监测外，如：额头、面罩、颈部、背部、衣服拉链、手臂、手指等，更衣认证还包括其它取样点。
- Routine monitoring may include garment samples from both forearms, and finger impressions from both hands. Overall profiles may also be evaluated. 常规监测包括两前臂的衣服样品和双手的指纹，亦可从整体进行评估。

g. Participation in media fills to demonstrate aseptic skill level. 培养基填充表明了无菌技术水平。

All training and certification activities should be documented and kept as part of the employee file. 所有培训和证书都必须记录下来，并作为员工个人档案予以保存。

4.5.3 Retraining 再培训

Gowning Certification 着装资格认证书

If samples from garment or finger impressions (dabs) exceed the alert/action level, the employee should be retrained on all appropriate procedures and re-certified before entry into the aseptic area is approved. 一旦发现衣服或指纹（dabs）高于警戒线或行动水平，工作人员便无法进入无菌区。他们必须按所有适当的程序进行再培训，等再次认证后方可批准进入。

*Routine Monitoring*常规监测

If samples from garment or finger impressions exceed the action level, it may require that the employee should be retrained on appropriate procedures and re-sampled at the earliest possible time. If a trend of over alert/action level occurrences develops, further corrective action, which may include complete re-certification or reassignment to new duties outside the aseptic area, may be considered. 如果衣服和指纹超过行动水平，这就需要工作人员按适当程序再次参加培训，并尽早重新采样。若其超过警戒线和行动水平呈上升趋势，就必须采取进一步的纠正措施，比如说进行完全的再验证，或在无菌区外重新分配任务。

Annual retraining and re-certification should occur for all employees required to work in an aseptic environment. In addition, all employees involved in aseptic manufacturing should participate in a process simulation test (media fill) at least annually. All retraining and re-certification activities should be documented and kept

as part of the employee file. 所有在无菌环境工作的人员每年都需再培训和再验证。此外，无菌生产区的全体成员每年至少要参加一次工艺模拟测试（培养基填充）。所有再培训和再验证活动都必须记录下来，并作为员工个人档案予以保存。

4.6 Product or Component Bioburden 产品或部件生物负荷

Product or component bioburden monitoring is not considered part of all environmental monitoring programs. Bioburden testing is performed on a non-sterile product to determine its microbial load. The intended use of the product, the nature of the product (growth promoting product which is held during processing), or the manufacturing process used may dictate the establishment of acceptance levels and the exclusion of objectionable microorganisms. Listed below are some factors that may impact product or component bioburden: 产品或部件生物负荷监测并不是所有环境监测项目的一部分。生物负荷测试在非无菌产品上进行，以确定其微生物负荷。产品的预定用途、性质（加工过程中促进产品成型）或制造工艺的使用均可决定其验收等级或对不良微生物的排除。以下列出的是可能会造成产品或部件生物负荷的一些因素：

- Raw material source: Bioburden may range from very high (derived from natural sources) to zero. 原料来源：生物负荷的范围很广，可以很高（源于天然资源），也可以为零。
- Water: It is often the highest volume raw material in product formulations. 水：水通往是产品配方中量最多的一种原料。
- Components: Various grade glass or plastic components can be obtained either sterile or non-sterile. 部件：各种高档玻璃或塑料部件可灭菌或未灭菌。
- Manufacturing environment: It should not adversely affect product quality. 生产环境：生产环境可能对产品质量产生不利的影响。
- Processing of formulation: Formulations incorporating filtration steps or requiring heating for dissolution may reduce bioburden. Other manufacturing steps such as timed storage at ambient temperature may increase bioburden. 配方工艺：将配方纳入过滤步骤，或者加热散发可能会降低生物负荷。而其他生产步骤，如在常温下将其定时存储则会增加生物负荷。
- Equipment: The equipment used and its level of cleanliness will impact final product bioburden. 设备：所使用设备的洁净程度会影响产品最终的生物负荷。

Antimicrobial activity: The presence of preservatives and the antimicrobial properties of the raw materials used will determine the formulation susceptibility to contamination. 抗菌活性：配方对污染的敏感度取决于防腐剂的存在和原材料的抗菌性能。

- Water activity: Water activity (a determinant in preservative selection) is an indicator of formulation susceptibility to contamination. 水活性：水活性（选择防腐剂的决定因子）是配方对污染的敏感度的标志。

4.6.1 Determination of Product or Component Bioburden 产品或部件生物负荷确认

Product or component bioburden levels may be determined through various test methods. Some methods are listed below: 产品或部件生物负荷级别可通过各种测试法来确定。方法如下：

Pour plating 倾倒电镀法
Spread plating延伸电镀法
Membrane filtration隔膜过滤法
Most Probable Number (MPN) 最大或然数法
Automated rapid microbiology systems自动化快速微生物系统法

The test method used will be based on the level of sensitivity necessary to: (a) meet the established acceptance criteria, and (b) neutralize any anti-microbial property that may be inherent to raw materials or as a result of added preservatives. Some automated rapid microbiology systems give higher counts than manual methods, since they may include counts of non-culturable or injured organisms. 测试使用的方法根据敏感度级别，需做到以下两方面：1）符合既定的验收标准 2）中和任何原料固有的或因添加防腐剂产生的抗菌性能。一些自动化快速微生物系统法比手工方法更高效，因为它们包括无数可培养或受伤的生物。

All relevant factors must be considered when establishing acceptance criteria for product and component bioburden. An acceptable bioburden level is that which does not adversely affect product quality. 在建立产品和部件生物负荷验收标准时，一切相关因素都必须考虑在内。一个可接受的生物负荷标准不影响产品质量。

For many terminally sterilized products, bioburden counts alone do not provide sufficient information. It also may be necessary to assess the thermoresistance, or D-value, of the bioburden. Total bioburden counts that are within limits may cause a significant problem if the bioburden exceeds the thermoresistance anticipated for the sterilization model. 对许多最终已灭菌产品来说，生物负荷数本身并不能提供足够的信息。同时，评估生物负荷的抗热性或D值也是必要的。如果总限度内生物负荷数超过灭菌模式预期的抗热性，将引发重要问题。

D-values can be determined using sophisticated equipment (thermoresistometer) with square wave heating, with heat-up and cooling times less than or equal to 10 seconds. For routine screening of bioburden, a heat shock or boiling water test can be used to rule out the presence of organisms exceeding a predetermined D-value. 使用先进的设备（热阻计）与方波加热便可确定D值，升温时间和冷却时间均不超过10秒。对于微生物负荷的常规筛选，一次热震或沸水测试即可排除超出预定D值的生物体。

4.6.2 Parametric Release and Bioburden 参数放行和生物负荷

The acceptance of parametric release by the FDA in 1985 increased the importance of bioburden testing, characterization, and resistance of recovered microorganisms. FDA Compliance Policy Guide 7132a.13 issued in 1987 details the necessary criteria for parametric release. As defined in the policy guide, parametric release is a sterility release procedure based upon effective control, monitoring, and documentation of a validated sterilization process cycle in lieu of release based upon end-product sterility testing. 1985年，美国食品及药物管理局于对参数放行的接受增加了生物负荷的测试、特性的重要性，以及复原微生物体的抵抗力。1987年实施的FDA认证政策指南中详细规定了参数放行的必要标准。政策指南中指出，参数放行是一套灭菌放行程序。它根据有效的控制和监测，以及一份有法律效力的灭菌工艺文件，替代了以终端产品灭菌测试来放行的方法。

Major emphasis is placed on the resistance of recovered spore formers. Recovered spore formers with greater resistance than the indicator organism used in the cycle validation would render the batch non-sterile in terms of the guidance. 现已非常重视复原的芽孢菌类阻力。循环验证中复原的芽孢菌类阻力比指示有机物大时，从指南方面来说此批为无菌。

4.6.3 In-Process Testing 过程中培训

In-process environmental monitoring samples may be taken to evaluate: 对过

程中环境监测样本可以采取如下评估：

- The ability of the equipment to perform within specified environmental quality standards设备能在规定的环境质量标准内完成
- Operator ability to maintain area cleanliness during process operations操作员能在工艺操作过程中保持作业区的整洁
- Effectiveness of cleaning for the facility and its equipment清洗整理设施设备的高效性

This monitoring is typically performed in areas and during operations where product is potentially exposed to environmental or operator contamination, however, it is not always included for closed systems since the results may not have a correlation to product impact. 监测通常在某区域，操作过程中产品可能遭受来自环境或人员的污染，但结果与产品并无相互联系，因此并不总是在封闭系统内进行。

Process-related monitoring may include surface and air sites near aseptic connections or product transfer steps. The manufacturing operations monitored may occur in an open room, under laminar flow, or within a "closed" system. Sites should be chosen to demonstrate process integrity in both "open" and "closed" processes. Sample sites and levels also should be chosen to provide meaningful data about a given operation. As an example, nonviable particle counts taken during loading of powdered media into a vessel in a Class 100,000 area may not provide data that is indicative of process quality. Non-viable particle counts taken during aseptic processing operations (excluding powders) in Class 100 areas may provide more valuable information about process control. 工艺相关监测可能包括接近无菌连接或产品转移处的表面和空气位置。生产监测可能发生在层流下的开放空间，或是在一个封闭系统内。位置的选择应能证明"开放"及"封闭"工艺的完整性。采样点和采样水平也应对指定操作能提供有意义的数据。例如，将粉末状介质装入10万级的容器中进行的非活性例子计数可能无法提供数据来表明工艺质量；但若在100级的无菌工艺中（除粉末外）进行计数，则可能对工艺控制提供更具价值的信息。

The subsequent purification/bioburden reduction steps in a process may also impact the degree to which in-processing testing is warranted. Test frequencies for batch-related, in-process monitoring may differ from those for routine area monitoring. In many cases, environmental monitoring performed in conjunction with batch production activities may fulfill the requirements for routine area monitoring. 工艺中随后的净化/生物负荷削减措施也在一定程度影响过程中测试。与批有关的过程中监测的测试频率不同于那些常规区域监测。在很多情况下，环境监测和批生产活动同时进行可以达到常规区域监测的要求。

Surface and viable air samples that select for the host organism may be appropriate in a fermentation/recovery process area. This data may help to demonstrate process integrity and/or cleaning effectiveness during a product changeover. 这些表面和活性空气样本的宿主生物体也很适合在过程领域中发酵/复原。这些数据有助于说明产品改变过程的完整性和/或清洗效果

The following table describes examples of different activities and possible sampling locations. The table is not meant to be all inclusive. 下表描述了不同活动及其可能的取样位置（不能涵盖所有）。

Process-related environmental monitoring activities and locations. 工艺相关的环境监测活动和选址

PROCESS工艺	**PROCESS ACTIVITIES TO CONSIDER MONITORING** 检测过程中的活动	**LOCATIONS TO MONITOR**监测地点
• **Fermentation/Primary Recovery**发酵/初次复原	• Inoculation of inoculum scale-up vessels 放大容器的培养 • Inoculation of fermenter 发酵罐培养 • Homogenization of harvest material收获材料的均化处理 • Product transfer operations (harvest of product) 产品转换工艺（产品的获取）	• Connection points on transfer lines 转换线上的连接点 • Near seals and gasket on fermenter发酵罐封孔和垫片附近 • Near pistons on homogenizer均质机活塞附近 • Near centrifuges离心机附近 • Sterile additions/sampling ports灭菌设备/采样端口
• **Purification**净化	• Loading of process vessels, chromatography columns 层析柱容器装载 • Collection of fractions 粒组的收集 • Pooling of fractions 粒组的合并	• Air and surfaces near process activities where the product is exposed to the environment 暴露在环境中的产品工艺活动的空气和表面附近 • Bench of laminar flow unit层流设备段 • Near fraction collection unit 粒组收集设备附近 • Loading port of chromatography column or ultrafiltration skid层析柱或超滤器装物口
• **Formulation**配方	• Loading of formulation vessel 配方容器的装载 • Addition of components during formulation配方时部件增加 • Sterilizing filtration process灭菌过滤工艺	• Opening of formulation vessel 配方容器口 • Point of aseptic connection from formulation vessel to sterile bulk tank从配方容器到灭菌散装罐的灭菌连接处
• **Filling and Finishing Operations**充填及完成操作	• Before filling (pre-fill) 充填前 • Fill line set-up安装充填输送管 • During filling充填过程 • Mechanical intervention on fill line 机器加入充填输送管 • Loading of lyophilizer装载冷冻干燥机 • After filling (post-fill) 充填完成	• Fill room and adjacent support rooms which constitute the aseptic suite 填充是和邻近的后备室 • Fill line at set-up during interventions干扰期间安装灌装线 • Areas of operator activity工作人员活动区 • Fill line during filling充填时的充填输送管 • Near container staging容器转运附近 • At the filling nozzles充填喷头处 • Near the stoppering mechanism胶塞机器附近 • At the lyophilizer loading door冷冻干燥机负荷门处 • HEPA-filtered transfer carts HEPA-过滤转移车处 • Fill line and aseptic suite surfaces post-fill 灌装线和无菌防护服表面 • Operator gowns and gloves at end of shift; include janitorial staff结束时操作员换衣服和

		手套

4.7 Environmental Monitoring During Routine Sterility Testing 常规无菌测试过程中的环境监测

Background 背景

Sterility testing facilities should be designed and operated in an equivalent manner to aseptic processing areas. Environmental monitoring should be conducted in an active mode during each shift, with alert and action limits set that are comparable to those used in aseptic process areas in the manufacturing plant. Monitoring should be conducted to demonstrate continuous microbial contamination control, consistent technician performance and to obtain information concerning the possible source of the microorganisms associated with sterility failures. 无菌测试设施的设计和操作应与无菌工艺区相同。环境监测应设为自动模式，以便在每一次转换时设置警戒和行动限制，这与生产车间无菌工艺区类似。应进行监测以证明连续微生物污染控制，持续的技术员执行并得到无菌故障相关的微生物可能来源的相关信息。

Air Monitoring 空气监测

Options include active samplers and/or settling plates. Air settling plates may be exposed on the work area during the sterility testing. 有自动采样和/或沉降板两种监测选项。空气沉降板在进行无菌测试期间可能会暴露在工作区。

Surface Monitoring 表面监测

The work surface and items that are not terminally sterilized should be routinely monitored using contact plates or surface swabs. 工作台面和物品在最后未灭菌，可通过接触板或表面拭子对其定期监测。

Personnel Monitoring 人员监测

Gloves and gowns of personnel conducting the sterility tests should be routinely monitored. 负责这次无菌测试的工作人员应戴上手套，穿上防护服并接受常规监测。

Trend Analyses 趋势分析

In general, the recommended guidelines for Class 100 aseptic processing area can be employed as action levels. Alert levels may be set using historic monitoring data. Trend analysis should be undertaken by sterility test location and sampling site. Corrective action, in terms of review of environmental controls, sanitization, and technician training should be standardized in response to out-of-trend results. The environmental monitoring data should be compared to the first-stage sterility failures by sterility test location, product, and sterility testing technician. 一般说来，建议将100级无菌工艺区可作为行动水平。警戒线可沿用使用过的历史监测数据。趋势分析应根据无菌测试地点和采样点。根据环境控制的纠错措施，卫生处理和技术培训，应作为对过时结果回答的标准与一级灭菌故障做比较。

5.0 VALIDATION/QUALIFICATION OF ENVIRONMENTAL MONITORING SYSTEMS 环境监测系统验证/确认

Under the scope of environmental monitoring, validation/qualification is required for classified environments and clean utilities, such as compressed gases and high purity water systems, depending upon the intended use. The specific validation requirements are specified in many regulatory and industry guidelines. For this document, validation and qualification are considered synonymous. 在环境

监测范围下，分级环境和洁净公用工程需要验证/确认，如取决于使用目的选择压缩气体和高纯水系统。具体的验证要求在许多规范和工业指南中有规定。对这种文件，验证也就是确认。

The validation requirements, including acceptance criteria, are typically described in procedures that are specific for each process or system being validated. An overview of some validation considerations is included in this section. 验证要求（含验收标准）通常按每种工艺和系统程序进行描述。此章节包括一些验证条件的概要。

When the process or equipment design is changed or replaced, a partial or full validation may be required before the process can resume. Routine monitoring usually can continue under the same conditions as those under the original validation. Some companies choose to perform periodic revalidation or requalification, while others manage through a change control process to determine when revalidation is required. 当工艺或设备设计改变或被替换时，在工艺确认前需作出部分或整体验证。常规监测在相同条件下通常能沿用，正如在原始验证下。当需要重新验证时，有些公司选择定期再验证或再确认，而其他一些管理者通过变更控制工艺来确定。

5.1 Environment/HVAC Systems 环境/空调系统

Testing of classified environments within which the aseptic filling process is performed is divided into two basic types: static and dynamic. Environmental validation testing under static and dynamic conditions is performed to determine the ability of the system to provide an environment of acceptable quality. 无菌灌装过程内，分级环境测试可分为静态和动态两种基本类型。在静态和动态条件下，环境验证测试的实行取决于提供环境验收系统质量的能力。

The static condition provides for the monitoring of the area with all HVAC systems in operation, with all equipment in place, and with no personnel present. Performance tests executed under static conditions serve as baseline information to demonstrate that the areas can maintain a high quality environment with no personnel activity. Static testing also ensures that the environment is of acceptable quality prior to dynamic testing. 静态条件提供的监测区域：所有空调系统在运转，设施在位，且无人在场。静态条件下进行的性能测试作为基线信息，证明无人员活动时区域可维持高质量环境。同时，静态测试保证在动态测试前的环境质量可接受。

Testing under dynamic conditions provides for the monitoring of the area with all HVAC systems in operation, equipment in operation, and operational personnel present. The dynamic testing demonstrates that the area can maintain a high quality environment during routine manufacturing conditions. Prior to validating the complete environment/HVAC system, it is assumed that the individual pieces of HVAC equipment have been validated. 动态条件下的测试监测区域：所有的空调系统和设备都在运行，操作员业在场。动态测试表明在正常操作条件期间，区域能够维持高质量环境。完整环境/空调系统验证前，假设单件空调设备已验证。

Typical tests include: 典型测试包括

a. Cleaning and sanitizing/disinfecting procedures utilize microbial surface monitoring to evaluate the effectiveness of the cleaning procedure to reduce the microbial level. (Cleaning and sanitization may be validated either separately or as part of the same protocol)
清洗和灭菌/消毒程序利用微生物表面监测来评估减少微生物水平的清洁程序的效果。（清洁和消毒既可单独验证，也可并作同一方案的一部分进行验证。）

b. Airborne non-viable particle count testing is performed to demonstrate that the manufacturing environment is maintained at a particle count level within the specified limits under both static and dynamic conditions. 空气中非活性粒子数的测试表明，在静态和动态条件下，规定限制内的操作环境可维持一定的粒子数。

c. Airborne viable particle count tests are performed to demonstrate that the airborne bioburden is within specified levels under both static and dynamic conditions. 空气中活性粒子数的测试表明，在静态和动态条件下，空气中的生物负荷在规定水平内。

Additional tests may be performed to verify the correct operation of the HVAC system and of the clean room. 额外的测试证明空调系统和洁净空间的操作正确。

5.2 Utilities 公用工程

Utility systems are usually qualified initially and again when a substantial change has taken place. Since most companies trend the data from these systems on an ongoing basis, periodic requalification is frequently not performed. Alternatively, there are periodic reports assessing the trending data. 通常，公用工程系统起初是合格的，然后发生重大改变。由于大多公司趋向从持续进行的系统中获得数据，经常不定期进行再确认。或者需有这些趋势数据评估的定期报告。

5.3 Validation of Aseptic Processes - Media Fills (Process Simulation Tests) 无菌工艺验证- 培养基填充（工艺模拟测试）

Media fills are useful in assessing the quality and process capability of aseptic process conditions and techniques in the manufacture of drug and diagnostic products by simulating aseptic processing, using microbiological growth media in place of product. Media fills are a good way to assess the total system for production and environmental monitoring. 培养基填充在评估药品和诊断药的无菌工艺条件和技术方面很有用。它通过模拟无菌工艺和使用微生物生长培养基代替一般产品来制造药品和诊断产品。培养基填充是评估整个生产和环境监测的好方法。

Initial performance qualifications are conducted to validate new products, processes, or changes to filling operations. Initial process simulation tests should be performed after equipment qualification and sterilization validation is completed. Environmental monitoring data must also show that the room is functioning in the desired level of control. At least the same level of environmental monitoring performed for production should be performed during a media fill. Some regulatory agencies have specified detailed lists of environmental data to be collected during the media fill. 初步性能确认用于验证新产品，工艺或填充作业的变更。在完成设备确认和灭菌验证后，方可进行初步工艺模拟测试。环境监测数据也必须表明房间在理想的控制水平内运作。至少在培养基填充过程中，应进行同样水平的环境监测。有些管理机构拥有在培养基填充过程中采集的环境数据具体清单。

Routine performance requalifications are required to be performed for each aseptic process and filling line as well as each container/closure system. Typically, routine media fills are performed at least every six months. All personnel who may be in an aseptic area should take part in a process simulation test at least annually. Effective aseptic processing programs need to address the following: 每个无菌工艺，灌装线和容器/密封系统需要进行常规性能再确认。一般情况下，常规培养基填充至少每半年执行一次。所有进入无菌区域的人员都应该参加工艺模拟测试，每年至少一次。有效的无菌工艺项目：

- Worst Case/Interventions 最差条件/干扰
- Media Growth Promotion Testing 培养基促生长测试
- Incubation duration, temperature, and orientation of filled units 培养时间，温度和填充部件方向
- Documentation程序说明书
- Acceptance Criteria验收标准
- Investigation and Corrective Actions调查和纠正措施

For additional details, the reader is referred to PDA Technical Report No. 22, "Process Simulation Testing for Aseptically Filled Products," PDA Technical Report No. 24, "Current Practices in the Validation of Aseptic Processing - 1996," PDA Technical Report No. 28, "Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals," the 1987 FDA *Guideline on Sterile Products Produced by Aseptic Processing,* and the 1994 FDA *Guidance for Industry for the Submission of Documentation for the Sterilization Process Validation in Applications for Human and Veterinary Drug Products.* 详情请参照：PDA技术报告第22期"无菌填充产品工艺模拟测试"；PDA技术报告第24期"无菌工艺验证通用法-1996"；PDA技术报告第28期"无菌原料药工艺模拟测试"；1987年，FDA《使用无菌工艺生产无菌产品指南》；1994年，FDA《提交灭菌工艺验证申请人兽药品产业说明书指南》

6.0 CONCLUSION 总结

The Task Force believes that this document can assist the reader in establishing the fundamentals of an environmental monitoring program related to facility control and compliance. Its intent was to serve as an aid in setting up a meaningful, manageable and defendable program. 专项小组认为，这份文件可以帮助读者建立设施控制和相符性相关的环境监测计划的基础。其目的在于帮助建立一个有意义、便于管理、有保障的计划。