Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities

无菌生产设施的清洁消毒程序原理

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1.0 Introduction 概述

While sterile product manufacturing has the most stringent application, these concepts can also be used to design a program for the manufacture of nonsterile products. To ensure a consistently controlled production environment, a comprehensive cleaning and disinfection program together with a contamination control program should be supported by the following:

尽管无菌药品生产具有很严格的应用，这些概念其实也可以用于设计非无菌药品的生产计划。为了确保对生产环境的控制保持一致，需要以下内容来支持综合清洁和消毒计划以及污染控制计划：

- Sound facility design and maintenance
- 合理的设施设施和维护
- Established documentation systems
- 建文件记录体系
- Validated/qualified disinfection procedures
- 验证/确认消毒程序
- Reliable process controls
- 可靠的工艺控制
- Good housekeeping practices
- 良好的清洁规范
- Effective area traffic and access controls
- 有效的区域交通和出入控制
- Effective training, certification/qualification, and evaluation programs
- 有效的培训、认证/确认和评估程序
- Quality assurance of materials and equipment
- 物料和设备质量保证
- Risk management mitigation
- 风险降低管理

The purpose of the cleaning and disinfection program is not only to control microbial contamination, but also to serve as a corrective action for the loss of control for viable excursions contamination.

清洁消毒程序的目的不仅仅是控制微生物污染，也是可能的污染失控时的纠正措施。

While the destruction of viable cells are an integral part of the cleaning and disinfection program, the use of disinfection as a singular focus without efforts to control contamination from entering the area is without technical merit. Environmental monitoring (EM) evaluates the efficacy of controls on the manufacturing environment. It is through control of bioburden levels entering the area, along with cleaning and disinfection, that acceptable viable control of the manufacturing or appropriate testing environment is achieved. This technical report provides

comprehensive information and suggested best practices as well as appropriate references to support such guidance.

摧毁活性细胞是清洁消毒程序不可分割的一部分，单纯地考虑消毒，而不去控制进入区域的污染是没有技术价值的。环境监测（EM）评估生产环境控制的有效性。通过对进入区域的生物负载水平的控制，以及清洁消毒，将生产或适当的测试环境控制在可接受水平。本技术报告提供全面的信息，并推荐了最好的做法以及适当的参考文件来支持本指南。

For individuals wanting a historical perspective of disinfection, a summary can be found in Appendix I (Section 17.0).

如果想要知道消毒的历史，可以在附录1中找到一个简述（第17.0部分）。

The technical report team consisted of members who are cleaning and disinfection experts from various global pharmaceutical and biopharmaceutical companies, academia, and companies that manufacture agents used in disinfection.

技术报告小组由来自全球不同制药和生物制药公司、学术机构和消毒用试剂生产公司的清洁消毒专家组成。

1.1 Purpose 目的

The purpose of this document is to identify systematic elements that are essential to assuring an appropriate and compliant cleaning and disinfection program for aseptic and bioburden controlled manufacturing facilities and classified environments.

本文的目的是识别出在无菌和生物负载受控的生产设计和分级环境下确保适当及符合要求的清洁消毒计划所必须的系统要素。

1.2 Scope 范围

The document covers cleaning and disinfection within controlled and noncontrolled environments using chemical agents that reduce or destroy microorganisms. The document provides guidance for non-product-contact surface cleaning and disinfection. This document is not intended to fully address product-contact surface cleaning from a clean-in-place (CIP) or clean-out-of-place (COP) system which is specifically addressed in PDA's *Technical Report No. 29 (Revised 2012): Points to Consider for Cleaning Validation* and *Technical Report No. 49: Points to Considerfor Biotechnology Cleaning Validation (1,2).*

本文包括了使用化学试剂对受控和非受控环境进行清洁消毒以减少或摧毁微生物内容。文件提供指南指导与产品不接受的表面的清洁消毒。本文件无意全面说明与产品接触的表面使用在线清洁或离线清洁系统所进行的清洁。这些情况在PDA第29号技术报告（2012年修订）“清洁验证考虑要点”和第49号技术报告“生物技术清洁验证考虑要点”中已有专门说明。

This document should be considered as technical guidance; it is not intended to establish any mandatory or implied standard.

本文应作为技术指南看待，它无意建立任何强制或暗示的标准。

2.0 Glossary of Terms 术语

Active Pharmaceutical Ingredient (API) 原料药

Any substance or mixture of substances intended to be used in the compounding of a drug preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity o other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.

意在用于药物制备，成为活性成分并具备药物活性或对人类和动物疾病诊断、治愈、缓解、治疗或防治，或影响身体功能和结构产生其它直接影响的所有物质或物质混合物，

Adverse Trend 不良趋势

A series of alert-level or action-level excursions that indicates the system or areas are not in control and have the potential to affect the product quality.

一系列接近警戒水平或行动水平的漂移，表示系统或区域不在受控状态，对产品质量有潜在影响。

Airlock 气闸

A room that controls the airflow between two rooms of different classification.

一个房间用以控制不同洁净级别两个房间之间的气流。

Analyte 分析物

Substance for which an analysis is being performed.

要进行分析的物质。

Antimicrobial Chemical Agent 抗菌化学剂

Substance used to destroy or suppress the growth of microorganisms, whether bacteria, fungi, or viruses, on inanimate objects and surfaces.

用于摧毁或抑制无生命对象和表面的微生物，可以是细菌、霉菌或病毒，生长的物质。

Area Disinfection 区域消毒

Disinfection of floors, walls, ceilings, and other surfaces.

对地面、墙面、天花板和其它表面的消毒。

Aseptic Processing Area (APA) 无菌工艺区域（APA）

A controlled environment that directly supports the aseptic processing of product consisting of several zones in which the air supply, materials, equipment, and personnel are regulated to control microbial and particulate contamination to acceptable levels.

直接支持产品无菌工艺的受控环境，由几个区域组成，其中有空气供应、物料、设备和人员受到规范管理以控制微生物和颗粒污染至可接受的水平。

Bioburden Load 生物负载

A measure of the number of viable organisms in a given environment or material.

对指定的环境或材料上活性生物数量的测量方式。

Change Control 变更控制

A documented system for reviewing proposed or actual changes that might affect a validated system or process; change control includes the determination of any corrective action required to ensure that the system remains in a validated state.

一种文件化系统，用于审核拟定的或实际的可能会影响已验证体系或工艺的变更。变更控制包括确定所需的纠正措施以确保体系维持在被验证的状态。

Clean (v.) 清洁（动词）

The implementation of procedures to render an area, piece of equipment, system, or object free of adulterants and contaminants.

在一个区域、一件设备、一个系统或一个对象上所实施程序使得其免于污染。

Clean(liness) 清洁（名词）

The measurement for the level of particulates, microbes, or other extraneous substances on an item or surface.

清除物体或表面颗粒、微粒或其它外来物质的措施。

Cleaning Agent 清洁剂

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

用于清洁工艺中清洗步骤的溶液或溶剂。清洁剂例子如水、有机溶剂、商业化学剂在水中稀释的，以及在水中稀释的配方清洁剂。

Colony-Forming Unit (CFU) 菌落形成单位（CFU）

The visible outcome of growth of microorganisms arising from a single or multiple cells.

一个或多个细胞中生长出的可见结果。

Contact Time 接触时长

The minimum amount of time that a sanitizer, disinfectant, or sporicide must be left in complete (wet) contact with the surface to be treated in order to be effective.

灭菌剂、消毒剂或杀孢子剂必须停留在全部湿润的被处理表面以达到效果的最短时长。

Contaminant 污染物

Any adventitiously or externally introduced material (e.g., chemical, biochemical, or microbial species) not intended to be part of the process.

偶然或外来引入的并不是工艺一部分的物质（例如，化学物质、生物化学物或微生物物种）。

Coverage 范围

The appropriate distribution of a chemical agent needed on the equipment surface to be effective.

在设备表面化学试剂产生效果的适当分布情况。

Degradation 降解

The breakdown (usually chemical) of material during manufacture, including during and after the cleaning process.

物料在生产过程中，包括在清洁过程前后的破坏（通常是化学破坏）。

Depyrogenation 去热源

Removal or destruction of pyrogens.

去除或摧毁热源。

Detergent 清洁剂

A synthetic wetting agent and emulsifier that can be added to a solvent to improve its cleaning efficiency.

可以加入溶剂中提高其清洁效果的合成湿润试剂和剂。

Disinfectant 消毒剂

A chemical or physical agent that reduces, destroys, or eliminates vegetative forms of harmful microorganisms but not spores.

一种化学或物理试剂，可以降低、摧毁或清除有害微生物组织但不是孢子的可生长形态。

Disinfection 消毒

The destruction of pathogenic and other kinds of microorganisms by thermal or chemical means.

采用热力学或化学方式摧毁有害菌和其它类型微生物。

Environmental Monitoring (EM) 环境监测（EM）

Describes the processes and activities that need to take place to characterize and monitor the quality of the environment.

为了解和监测环境质量所进行的过程和活动。

First Air

Refers to the air exiting at the face of HEPA filters. Based on the airflow through HEPA filters and its unidirectional air flow the air exiting at the filter face is for the purpose of aseptic processing free of particulate contamination (both viable and non-viable).

指存在于HEPA过滤器表面的空气。根据通过HEPA过滤器的气流及其非直流气流，在过滤器表面的空气是为了清除颗粒污染的无菌处理（活性和非活性）。

Heating, Ventilating, and Air-Conditioning (HVAC) 暖通和空调（HVAC）

Refers to technology of indoor and automated environmental control.

指室内自动环境控制技术。

High-Efficiency Particulate Air (HEPA) Filter 高效空气过滤器（HEPA）

A type of air filter that must satisfy certain standards of efficiency such as those set by the United States Department of Energy (DOE). The air filter must remove 99.97% of all particles greater than 0.3 micrometer from the air that passes through it.

满意特定标准的一类空气过滤器，其效果由美国能源部（DOE）规定。该空气过滤器必须能滤除通过该过滤器空气中99.97%大于0.3μm的颗粒。

Gamma Irradiation 伽玛辐射

The process by which a material is rendered sterile by exposing the material to a radioactive source, such as Cobalt 60.

将物料暴露于一个辐射源，例如钴60，来进行灭菌的过程。

Germicide 杀菌剂

A compound that destroys all vegetative microorganisms.

一种摧毁所有能生长的微生物的化合物。

In-Use Testing (also called In-Situ Testing) 原位试验

A field study that validates the effectiveness of a disinfecting agent, the trained operators, and the approved operating procedures.

一种现场研究，用来验证消毒剂、培训过后操作员和批准的操作程序的有效性。

Isolates 分离

Microorganisms that are recovered from a facility.

从设备上回收的微生物。

Largest Daily Dose 最大日服用剂量

Maximum daily dose of the next product to be produced in the equipment train. Median lethal dose, or median lethal concentration, of a toxin, radiation, or pathogen; the dose required to kill half the members of a tested population after a specified test duration. LDm figures are frequently used as a general indicator of a substance's acute toxicity.

在同一设备链中要生产的下一药品的最大日服用剂量。一种有毒物、辐射或致病菌的半数致死量，或半数致死浓度；在指定的测试期间杀死半数受试生物所需的剂量。LDm数通常用作物质急性毒性的常规指标。

Log Reduction 对数下降

Log reduction is defined as the first log being 90%, the second log being 9% and the third log being 0.09% of the original inoculums.

对数指第一对数为最初接种数量的90%，第二对数为9%，第三对数为0.09%。

Manual Cleaning 手动清洁

A cleaning procedure requiring operator-performed critical steps (e.g., scrubbing with a brush or rinsing with a hose).

需要操作人员进行关键操作的清洁程序（例如，使用刷子刮除或使用水管冲洗）。

Metabolite 代谢物

A substance that is either the result of metabolism or a requirement for a metabolic process.

代谢过程所需或所产生的物质。

Mycoplasma 支原体

Small, flexible bacteria that lack a cell wall. Mycoplasma can pass through 0.2 µm and some 0.1 µm rated filters and are unaffected by some antibiotics, such as penicillin.

没有细胞壁的很小的会变形的细菌。支原体可以通过0.2µm和一些0.1µm过滤器，并且不受到抗菌剂的影响，如青霉素。

Penicylinder 空心玻璃筒

A small, ceramic carrier surface used to hold cultures of microorganisms. Used in antimicrobial effectiveness testing procedures.

很小的、陶瓷载体表面用于微生物培养。用于抗菌效果测试。

Pesticide 杀虫剂

Any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. Any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant and any nitrogen stabilizer.

用于防止、摧毁、驱除或减少害虫的物质或物质混合物。用作工厂调节、脱叶或干燥剂和其它氮稳定剂的物质或物质混合物。

Pyrogen 热源

A material that elicits a pyrogenic response (fever).

导致发热反应（发烧）的物质。

Sanitize 消毒

To make physically clean and to remove and destroy, to the maximum degree that is practical, agents injurious to health.

进行物理清洁、以及清除和摧毁对健康有害的试剂至最大可行程度。

Sanitizer 消毒剂

A compound that will reduce the number of vegetative microorganisms to a safe level as determined by public health requirements. Normally a reduction of 10^3 in vegetative microorganisms is obtained.

将活性微生物数量降低至公共安全要求确定的安全水平的化合物。通常达到活性微生物降低至千分之一的水平。

Sonicate 声波降解标本

To use sound energy to agitate particles; generally used to accomplish mixing or cleaning.

使用声波能量搅动颗粒，通过用于完成混合或清洁。

Sporicide 杀孢子剂

A compound that destroys all vegetative microorganisms and bacterial and fungal spores.

摧毁所有活性微生物和细菌及霉菌孢子的化合物。

Sterile 无菌

The absence of viable microorganisms.

没有活性微生物的状态。

Sterilization 灭菌

A process by which something is rendered sterile (i.e., moist heat, dry heat, chemical, irradiation); normally validated at 10^6 organism reduction.

使某物达到无菌的处理过程（即，温热、干热、化学、辐射），通常经过验证达到存留率为原微生物百万分之一。

Substrate 基质

Primary construction material of a surface to be cleaned or disinfected.

要清洁或消毒的表面的基底材料。

Total Organic Carbon (TOC) 总有机碳（TOC）

Measurement term for the total organic carbon in a sample.

一个样品中有机碳测量项目。

Transfer Disinfection 转移消毒

A disinfection process conducted on materials and equipment that coats the surface for a validated wetted time to remove bioburden prior to introducing such items into classified areas.

将要消毒的物料或设备表面覆盖持续经过验证的湿润时长以清除生物负载，然后将该物料移入洁净区的消毒过程。

Trend Analysis 趋势分析

Analysis of environmental data over time indicating a shift; adverse trends require investigation.

对一段时间环境数据进行的分析，不良趋势要进行调查。

Vapor Phase Hydrogen Peroxide (VPHP) 汽相过氧化氢（VPHP）

A disinfection system in which 35% hydrogen peroxide is changed to a vapor phase and used for bioburden reduction of a chamber or items in a chamber.

一种消毒系统，采用35%过氧化氢，将其变为气相，用于降低柜中或柜里的物品的生物负载。

Validation 验证

A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a results meeting predetermined acceptance criteria.

高度保证指定的工艺、方法或系统能持续产生出符合预定可接受标准的结果的文件化程序。

Visually Clean 目视清洁

Absence of materials that would adulterate a product when inspected with the eyes.

肉眼检查时发现没有会污染产品的物料。

3.0 Sanitizer, Disinfectant, and Sporicide
灭菌剂、消毒剂和杀孢子剂

Claims and Classifications 声明和分类

Sanitizers, disinfectants, and sporicides are chemicals agents that reduce, eliminate, or destroy microorganisms.

灭菌剂、消毒剂和杀孢子剂是减少、清除或摧毁微生物的化学试剂。

Registration testing of these chemical agents to meet the requirements of organizations such as the U.S. Environmental Protection Agency (EPA), EU Biocidal Directive, Australian Therapeutics Goods Administration (TGA), Health Canada, and many others are performed at very high levels to address the high-bioburden environments in which they may be used. High-bioburden environments include hospitals, food processors, clinical laboratories, institution, consumer, and others.

这些化学试剂的注册测试要符合一些组织的要求，例如美国环境保护署（EPA）、欧盟生物杀灭指令、澳大利亚治疗产品管理局（TGA）、加拿大卫生局和许多其它机构，在很高水平上说明可能会使用的高生物负载环境。高生物负载环境包括医院、食品加工商、临床实验室、研究所、消费者和其它。

Registration and approval are required prior to sale in the marketplace and are defined by regulatory requirements in most every county. The label claims seen on product are approved in this fashion.

在大多数国家，需要根据法规要求进行注册和批准，然后才可以上市销售。产品上的标签声明也采用这种方式进行批准。

See Appendix II for additional information on registration of sanitizers, disinfectants, and sporicides.

参见附录2关于杀菌剂、消毒剂和杀孢子剂的更多注册信息。

Testing for the use of these same chemical agents in GMP manufacturing operations also requires testing prior to use. However, this testing is significantly different, as the bioburden load within a clean room environment is much lower. As such, the testing is performed with lower bioburden levels, decreased dry (wetted) time periods, and on varying substrates. This type of testing or internal qualification (performed by the firm who intends to use the product or by a third party contract laboratory) is an expectation of drug regulatory agencies worldwide such as the U.S. FDA, the European EMEA, and health ministries throughout the world and may be reviewed as part of the inspection process.

这些相同的化学试剂在GMP生产运行中的使用测试也需要在使用之前进行测试。但是，该测试有很大不同，因为在洁净间环境里的生物负载会更低。因此，此测试在较低的生物负载水平下进行，干燥（湿润）时长减少，并在不同基底上进行。此类测试或内部确认（由想使用此产品的公司或由第三方合同实验室实施）是全球药监机构的要求，如美国FDA、欧洲EMEA以及全球卫生管理部门，可能会被作为检查内容的一部分。

Sanitizers can best be described as chemical agents that reduce the number of vegetative microorganisms to a safe level but do not destroy bacterial and fungal spores. Disinfectants are chemical agents that reduce, destroy, or eliminate vegetative forms of microorganisms but not spores. Sporicides are chemical agents that will destroy all vegetative microorganisms as well as bacterial and fungal spores.

准确地说，杀菌剂是减少活性微生物数量至安全水平的化学试剂，但并不摧毁细菌和霉菌孢子。消毒剂是减少、摧毁或消除活性微生物但不是孢子的化学试剂。杀孢子剂则会摧毁所有活性微生物以及细菌和霉菌孢子的化学试剂。

However, time frames to destroy high levels of vegetative microorganisms and spores may be extensive and reach far beyond the bioburden level and normal dry (wetted) times characteristic of the clean room operation.

但是，摧毁高水平活性微生物和孢子的框架时间可能会差异很大，大大超出洁净间运行的生物负载水平和常规干燥（湿润）时长特性。

The classifications of sanitizers, disinfectants, and sporicides include the following:

杀菌剂、消毒剂和杀孢子剂类别包括以下：

- Alcohols
- 乙醇
- Chlorine and sodium hypochlorite
- 氯和次氯酸钠
- Iodine/bromine-containing compounds
- 含碘/溴化合物
- Peracetic acid/hydrogen peroxide
- 过氧乙酸/过氧化氢
- Aldehydes
- 醛类
- B-Propiolactone
- b-丙酸内酯
- Quaternary ammonium compounds
- 季胺类化合物
- Ethylene oxide
- 氧化乙烯
- Phenolic
- 酚类
- Ozone
- 臭氧
- Hydrogen peroxide
- 过氧化氢
- Chlorine dioxide
- 二氧化氯

The term "disinfectant" is often used as a general term as well as a term referring to a specific type of chemical agent. To avoid confusion, in this document the term *antimicrobial chemical agent* will be used when referring to sanitizers, disinfectants, and sporicides in general.

术语“消毒”通常用作常规术语，也表示特定类型的化学试剂。为了避免混淆，在本文中术语“抗菌化学试剂”只有在指代常规消毒剂、灭菌剂和杀孢子剂时才使用。

4.0 Regulatory Expectations 法规要求

4.1 Regulations and Guidance 法规和指南

Reference to the cleaning and disinfecting of manufacturing areas can be found in regulations and guidance documents from various regulatory and standard-setting organizations. Listed below are citations from U.S. regulations and guidances, EU guidances, the PIC/s Convention, the U.S. Pharmacopiea, and the ISO.

不同法规和标准设定机构的规定和指南文件中可以找到生产区域清洁消毒的参考内容。下列内容是从美国法规和指南、欧盟指南、PIC/S委员会、美国药典和ISO中引用的。

- CFR Title 21 Part 211.42(c), (clOi), (clOv) *(3):*
- *美国联邦法规第21部分211章*

  Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of... (c)

  *操作应在具有足够大小的特定区域内完成。*应有分隔的或指定的区域或此类其它控制系统用于公司操作，以防止……过程中的污染或混淆

  Floors, walls and ceilings of smooth, hard surfaces that are easily cleanable (clOi)

  地面、墙面和天花板等平滑的硬表面易于清洁

  A *system for cleaning and disinfecting the room and equipment to produce aseptic conditions* (clOv)

  一个清洁和消毒房间和设备的系统用于生产无菌条件

- U.S. FDA, *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practices,* section X. Laboratory Controls: Sanitization Efficacy *(4):*
- 美国FDA，行业指南：采用无菌工艺生产的无菌药品---CGMP，第X部分，化验室控制：杀菌有效性（4）

  The suitability, efficacy, and limitations of sanitization agents and procedures should be assessed.

  灭菌剂的稳定性、效用和限制及程序应进行评估。

- EU *Human and Veterinary Medicinal Products,* Annex 1, *Manufacture of Sterile Medicinal Products (J):*
- EU 人药和兽药，附录1，无菌药品生产（J）

  In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

  在洁净区，所有暴露表面均应平滑、不可渗透、不会断裂，以最大程度减少颗粒或微生物脱落和滋生，使得重复使用清洁剂和消毒剂成为可能。

- The Pharmaceutical Inspection Convention (PIC/S) *Guide to Good Manufacturing Practices for MedicinalProducts (6):*
- PIC/S“药品GMP指南”

  Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in

general, any adverse effect on the quality of products. (Part I Chapter 3, Premises and Equipment)

*设施和设备的安放、设施、结构、使用和维护必须适用于其既定操作。*其平面和设计必须能最大程度减少人为错误的风险，允许进行有效清洁和维护，以避免交叉污染、粉尘和灰尘累积，以及所有对产品质量的不良影响（第1部分第3章，设施和设备）。

Using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination. (Chapter 5, Production)

使用已知有效的清洁和防污染程序，因为对设备的无效清洁是交叉污染的常见来源（第5章，生产）。

- The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Part 1 Chapter 3: Premises and Equipment *(7):*
- 欧盟药事法第4卷EU 人药和兽药GMP指南第1部分第3章：设施和设备

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

设施和设备的安放、设施、结构、使用和维护必须适用于其既定操作。其平面和设计必须能最大程度减少人为错误的风险，允许进行有效清洁和维护，以避免交叉污染、粉尘和灰尘累积，以及所有对产品质量的不良影响。

- The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Part 1 Chapter 5: Production *(8):*
- 欧盟药事法第4卷EU 人药和兽药GMP指南第1部分第3章：生产

Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3. This should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes to control risk of cross-contamination.

交叉污染必须通过第3章所述的设施和设备的设计来防止。这需要由工艺设计，和所有相关技术或组织措施的实施来支持，包括有效的或重复的清洁过程来控制交叉污染。

- USP <1072> Disinfectants and Antiseptics *(9):*
- 美国药典<1072>消毒和灭菌

A *sound cleaning and sanitization program is needed for controlled environments used in the manufacture of Pharmacopeial articles to prevent the microbial contamination of these articles. Sterile drug products may be contaminated via their pharmaceutical ingredients, process water, packaging components, manufacturing environment, processing equipment, and manufacturing operators*

在药品生产中所用的受控环境需要合理的清洁和灭菌程序，以防止这些物品受到微生物清洁。无菌药品可能会通过其药物成分、工艺用水、包装物、生产环境、工艺设备和生产操作人员受到污染。

- International Organization for Standardization (ISO) 13408-1, Aseptic Processing of Health Care Products; and ISO 14698, Cleanrooms andAssociated Controlled Environments—Biocontamination Control *(10,11):*
- 国际标准化组织（ISO）13408-1，保健产品无菌工艺；和ISO14698，洁净区和协同受控环境---生物污染控制

> *This part of ISO 14698 establishes the principles and basic methodology of a formal system of biocontamination control (Formal System) for assessing and controlling biocontamination when cleanroom technology is applied for that purpose. This part of ISO 14698 specifies the methods required for monitoring risk zones in a consistent way and for applying control measures appropriate to the degree of risk involved. In zones where risk is low, it can be used as a source of information.*
>
> *ISO14698的本部分建立了生物污染控制正式系统的原则和基本方法学，用以洁净区技术应用于此时的评估和控制生物污染。ISO14698的本部分指出了采用统一方法监测风险区域所需的方法，以及应用适当的控制措施来对风险评级的方法。在风险相对较低的区域，可以用作一种信息来源。*

These documents are general in nature, providing a limited amount of information on how cleaning and disinfection are to be executed but do convey the expectation that these programs are in place. The responsibility of proving the effectiveness of the chemical agents used remains with the individual firms.

一般来说，这些文件提供有限数量的如何实施清洁消毒的信息，只是要求具备这些程序。公司有责任证明提供所用化学试剂有效性。

4.2 Regulatory Inspections 法规检查

Due to their importance and direct impact on manufacturing operations, the cleaning and disinfection programs have been and continue to be a focus during regulatory inspections. Key components of any cleaning and disinfection program, which are often reviewed during inspections, include the following:

鉴于其重要性，以及其对生产运作的直接影响，清洁消毒程序在以前和以后都会是法规检查的焦点。在检查过程中通常会审核的清洁消毒程序的关键要素包括以下：

- Qualification of suppliers and agents
- 供应商和试剂确认
- Cleaning and disinfection methodologies
- 清洁和消毒方法学
- Decision to use ready-to-use vs. ready-to prepare chemical agents as well as the quality of water to be used (if needed) during their preparation
- 使用现配现用VS直接使用的化学试剂的决策，以及在制备过程中使用的水（如需要）的质量
- Process used for sterile filtering of antimicrobial chemical agents
- 用于抗菌化学试剂无菌过滤的过程
- Sterilization and storage of antimicrobial chemical agents used in aseptic processing areas
- 灭菌和无菌工艺区域所用的杀菌化学试剂的存贮
- Sterilization and storage of cleaning equipment (sprayers, buckets, mop heads, and mops)
- 灭菌和清洁设备的存贮（喷雾器、桶、抹布头和抹布）
- In-use expiration dating of antimicrobial chemical agents
- 杀菌化学试剂的使用有效期
- Rotation of agents
- 试剂轮换
- Training, qualifications, and responsibilities of personnel and supervisors

- 人员和监管者培训、确认和职责
- Frequency of cleaning and disinfection
- 清洁和消毒频次
- Contact times (wetted period)
- 接触时长（湿润时长）
- Method for addressing residuals
- 残留评估方法
- Documentation for cleaning and disinfection
- 清洁消毒文件记录
- Hold times for cleaned and disinfected areas and equipment
- 已清洁水系区域和设备保持时长
- Hold times for soiled areas and equipment
- 脏区域和设备的保持时长
- Cleaning and disinfection performed after a shutdown or an excursion
- 停产或发生偏差后实施的清洁消毒

While the preceding list may not be complete, it serves as a basis for the program and for inspection readiness.

之前的清单可能并不是完整的，它只是作为清洁消毒计划的基础，以及为了检查的准备而给出。

5.0 Qualification of New Suppliers and Agents
新供应商和试剂确认

New suppliers and new antimicrobial chemical agents for use in the disinfection program should be qualified prior to use following established procedures. A satisfactory audit, qualification testing, and a clearly defined Certificate of Analysis (CoA) are important aspects to be considered as part of the qualification. If changes occur in the agent's formulation, packaging, or manufacturing site, an evaluation should be performed to determine if requalification is required.

用于消毒程序的新的供应商和新的杀菌化学试剂应在使用前根据建立的程序进行确认。令人满意的审计、确认测试和清楚定义的检验报告（COA）被认为是确认中的重要部分。如果试剂的配方、包装或生产场所有所变更，则应进行评估以确定是否需要重新确认。

When choosing a new antimicrobial chemical agent from a supplier, evaluate the supplier's:

在从一个供应商处选择一个新的杀菌化学试剂时，要评估供应商的：

- Product literature/technical data
- 产品文字/技术数据
- Material safety information
- 物料安全信息
- Material compatibility
- 物料相容性
- Compatibility information
- 相容性信息
- Storage conditions
- 存贮条件
- Packaging presentations
- 包装
- Expiring dating
- 有效期
- Disposal requirements
- 处理要求
- Efficacy data
- 有效性数据
- Sterility and sterilization information (if the product is provided sterile)
- 无菌和灭菌信息（如果产品是作为无菌产品）

In evaluating supplier information related to the efficacy of an antimicrobial chemical agent, it is important to understand the testing methodology and standards used. These often vary depending on where the agent was

registered and the claims made regarding its use. See Appendices II-V for more information on this topic as well as safety-related information.

在评估关于杀菌化学试剂有效性的供应商信息时，了解所用的测试方法和标准非常重要。这些通常根据试剂注册地不同，以及关于其用途的声明而有差异。参见附录2-5，有关于此主题更多信息以及与安全相关的信息。

Depending on the specific use of the antimicrobial chemical agent and experience with the specific supplier, an audit may need to be performed. Extra attention should be given to the following during an audit:

根据杀菌化学试剂的特定用途和特定供应商的经验，可能需要进行审计。在审计中需要注意以下方面：

- Environmental control and cleaning of the manufacturing or packaging area and equipment used to manufacture the antimicrobial chemical agent.
- 用于生产杀菌化学试剂的生产或包装区域和设备的环境控制和清洁
- Control and disinfection or sterilization of the antimicrobial chemical agent packaging containers.
- 杀菌化学试剂包装容器的控制和消毒或灭菌
- Documentation and review of antimicrobial chemical agent production processing activities.
- 杀菌化学试剂生产处理活动的文件记录和审核
- For aseptically filled agents, the environmental monitoring (EM) program data, including alert and action levels, trending, corrective actions taken, and the use of neutralizing agents for the EM media used.
- 对于无菌灌装试剂，环境监测（EM）程序数据，包括警戒限和行动限、趋势、所采取的纠正措施以及所用EM培养基的中和剂使用
- For agents labeled as sterile, sterility testing data and qualification of the sterilization process.
- 对于标识为无菌的试剂，无菌测试数据和无菌工艺确认
- Water systems and the quality of water used in the manufacturing process.
- 水系统和工艺用水的质量
- Package or container integrity studies.
- 包装或容器完整性研究
- For double- and triple-bagged containers, disinfection of filled container and overwrapping integrity.
- 对于双层或三层袋装容器，灌装容器消毒和外包装完整性
- For double- and triple-bagged containers where a claim of sterility is made for inner bags, qualification of the sterilization process used.
- 对于双层和三层袋装容器，如果内袋有无菌声明，所用的灭菌过程的确认
- Handling and storage of finished product containers or work in progress.
- 成品容器或中间产品的处理和存贮
- Study results to support label claim of agent.
- 支持试剂标签声明的研究结果
- Documentation related to regulatory approval of agent.
- 与试剂法规批准有关的文件记录

- Change control: customer notification of ingredient changes or process changes that would affect the finished product—for example, wrapping, irradiation, and sterilization.
- 变更控制：会影响成品，例如，包装、辐射和灭菌，的成分变更或工艺变更时对客户的通知

5.1 Qualification Testing 确认测试

Qualification testing of a new antimicrobial chemical agent should include both laboratory and insitu testing. Chemical analysis of the actives and microbial efficacy testing should be performed.

对一个新的抗菌化学试剂的确认测试应包括化验室和现场测试。要进行活性化学分析以及微生物有效性测试。

Chemical analysis of the actives may be provided by the vendor or, alternatively, performed in-house or by a qualified contract laboratory using the vendor's method. Microbial efficacy testing, whether in suspension or in carrier studies, should be performed in-house or by a qualified contract testing laboratory.

活性化学分析可以由供应商提供，或者内部测试，或由一个经过确认的合同化验室使用供应商的方法进行测试。微生物有效性试验，如果是在混悬液中或在载体研究中，应内部进行测试，或由经过确认的第三方化验室进行测试。

The antimicrobials chemical agents used for testing should be close to or beyond their stated in-use expiration date (this should take into account a ready to use and/or a use dilution prepared from a concentrate expiry). Testing should be done in replicate on multiple lots of the antimicrobial chemical agent where applicable. It should be noted that significant registration testing on multiple lots of the agent is performed by the company registering the product to ensure product consistency between lots and stability throughout the stated shelf life.

用于测试的抗菌化学试剂应邻近或超出其使用有效期（这里要考虑直接使用和/或稀释使用时浓缩液的有效期）。如果可以的话，应对多个批次进行平行测试。要注意的是对多批试剂的重要的注册测试是由注册公司来进行的，以确保产品不同批次之间的一致性，以及其所声明的整个货架期的稳定性。

Additional qualification may be performed if changes in product formulation or packaging or site investigations deem it necessary. Information supporting the qualification includes the following seven areas:

如果生产配方或包装进行了变更，或现场调查认为必要时，可能需要进行再次确认。支持确认的信息包括以下七个方面：

- Description of packaging, label, and container type
- 包装、标签和容器类型描述
- Description of ingredients and concentrations
- 成分和浓度描述
- Lot or batch number
- 批号
- Efficacy testing results
- 有效性测试结果
- Irradiation or other sterilization verification certification
- 辐射或其它灭菌确认认证
- Safety data sheet information

- 安全数据信息表
- Disposal information
- 处理信息

5.2 Efficacy Testing 有效性测试

The demonstration of antimicrobial chemical agents to provide their respective kills is a function of the concentration of microorganisms present, the type of microorganisms, the choice of agent, the concentration of the agent, the porosity or texture of the surface to be cleaned, the method of application, and the contact time. Routinely, the agent used should be effective against the normal microbial vegetative flora recovered from the facility. Many efficacy testing guidelines, such as the Association of Official Analytical Chemist (AOAC), suggest high microorganism inoculum levels requiring longer contact times to destroy the population of cells (see Appendix VI, Section 22.0). As the normal clean room bioburden level is very low, the inoculum levels for testing would ideally depict levels seen in the controlled area. As this would not be practical in a test environment a higher inoculum level should be used and should not exceed 105. The antimicrobial chemical agent used within the industry can be broken into three general areas: sanitizers, disinfectants, and sporicides.

抗菌化学试剂杀灭效果是被杀灭微生物浓度、微生物类型、试剂选择、试剂浓度、要清洁的表面的孔隙度或质地、所使用的方法以及接触时长的函数。一般来说，所用的试剂应对从设施中回收到的常规微生物植物群落有效。许多有效性测试指南，例如美国分析化学家协会（AOAC），建议高浓度微生物接种需要更长的接触时长以摧毁细胞群（参见附录6第22.0部分）。由于常规洁净间生物负载水平非常之低，测试的接种水平理想地描述了受控区域所见水平。由于这种情况在测试环境中不现实，需要使用更高的接种水平，应超出105。行业内所用的抗菌化学试剂可以分为三个常规区域：灭菌剂、消毒剂和杀孢子剂。

- **Sanitizers 灭菌剂**

Sanitizers provide minimal reduction in thirty seconds to ten minutes and are often used for low levels of vegetative microorganisms. The type of sanitizer will dictate the appropriate contact time required. Alcohol is an example of a commonly used sanitizer.

杀菌剂提供在30秒到10分钟最小减少量，通常用于低水平的植物性微生物。灭菌剂的类型决定了所需适当的接触时长。乙醇是常用的灭菌剂的例子。

- **Disinfectants 消毒剂**

Disinfectants exhibit a higher level of efficacy than sanitizers, and their kill is dependent on the inoculums and the contact time. Disinfectants will typically kill vegetative microorganisms with the exception of spore-forming microorganisms. Examples include quaternary ammonium compounds and phenolics.

消毒剂比灭菌剂具有更高的有效性，其杀灭性与接种水平和接触时长无关。消毒剂一般会杀灭植物性微生物，孢子形态除外。消毒剂例子包括季胺盐和酚醛物。

- **Sporicides 杀孢子剂**

Sporicides provide up to a total kill depending on the inoculums and the wet contact time and will kill bacterial spore formers as well as mold. Products commonly used today include bleach, hydrogen peroxide, and a mixture of hydrogen peroxide and peracetic acid.

杀孢子剂提供全面杀灭性，其杀灭能力与接种水平、湿润接触时长有关，能杀灭细菌孢子形态以及霉菌。现今常用产品包括漂白剂、过氧化氢、过氧化氢和过氧乙酸混合物。

In general, contact or dry times in qualification studies should not exceed 120 seconds for alcohols (70% isopropanol and 70% denatured ethanol) and 10 minutes for disinfectants and sporicides. Longer contact times

may be required based on the specific chemical agents used.

一般来说，在确认研究中接触时长或干燥时长，乙醇（70%异丙醇，和70%变性乙醇）应超过120秒钟，消毒剂和杀孢子剂应超过10分钟。如果所用的是特定的化学试剂，可能需要更长的接触时长。

Methods to demonstrate efficacy include in-suspension and surface carrier (coupon) studies. In general, a total of three antimicrobial chemical agents (sanitizer, disinfectant, or sporicide) are all that would be qualified within the typical biopharmaceutical or pharmaceutical facility. While historically it was thought that a wide array of disinfectants were required to minimize the buildup of facilityresistant microorganisms, this is no longer a widely held belief (see Section 11.0).

证明有效性的方法包括悬浮液和表面载体（样本）研究。一般来说，三种抗菌化学试剂（杀菌剂、消毒剂或杀孢子剂）的总合都要在典型的生物药品或药品设施里进行确认。历史上曾经有过想法需要宽范围的消毒剂来最大程度减少设施耐药菌的累积，但现在这种想法已不再广泛流行了（参见第11.0部分）。

5.2.1 In-Suspension Studies 悬浮液研究

The in-suspension studies may be used to quickly screen various chemical agents to determine which may be the most effective. However, these types of studies should not be considered a replacement for carrier/coupon surface studies (discussed in Section 5.2.2) in determining antimicrobial chemical agent performance on clean room surfaces. The test may also be used, where applicable, to demonstrate an agent's efficacy in destroying suspended organisms in solutions (for tanks, holding vessels, bioreactors, etc.).

悬浮液研究可以用于快速筛选不同的化学试剂，确定哪种更为有效。但是，这类研究不能替代载体/样本表面研究（在5.2.2部分讨论），用以确定抗菌化学试剂在洁净间表面的性能。适当时，测试也可以用于证明试剂摧毁溶液中悬浮有机组织的有效性（罐、贮糟、生物反应器等）。

For in-suspension studies, a panel of six to ten microorganisms, including bacteria, yeast, and mold, should be used. Selection of organisms should be based on the type of environmental isolates recovered from the facility (environmental isolates are preferred); however, if facility isolates are not available ATCC cultures (or cultures from other recognized international culture collections) representing facility isolates are acceptable until facility isolates can be obtained. From the panel, the microorganisms chosen for each study should correlate with the type of antimicrobial chemical agent being evaluated (sanitizer, disinfectant, or sporicide).

对于悬浮液研究，应该使用6-10个微生物的对照，包括细菌、酵母菌和霉菌。生物的选择应根据从设施上回收的环境中分离物类型（最好是环境的分离物）。但是，如果设施分离物不能获得，也可以使用能代表设施中分离物的ATCC培养物（或从其它认可的国际菌种汇总中的培养物），直到设施分离物可以获得为止。通过对照，将每个研究中选择的微生物与要评估的抗菌化学试剂（消毒剂、灭菌剂或杀孢子剂）类型相关联。

One method that may be used to complete the studies is described here:

可以用于完成研究的一个方法描述如下：

1. A fresh culture of each organism is prepared to a known CFU/ml concentration.
   每个微生物新鲜培养至已知CFR/ml浓度。
2. For each organism, a small volume of the culture is transferred directly into a sterile preparation of the chemical agent and mixed. (An inoculum level of 10^3 to 10^4 is suggested.)
   每个微生物，直接转移一个较小体积至无菌制备的化学试剂中，混合（建议接种浓度为10^3-10^4）
3. The mixture is allowed to sit for a specified time to simulate the desired chemical agent contact (wetted) time.
   混合物静置一定时长，模拟所需的化学试剂接触（湿润）时长。
4. Once the desired time has been reached, the entire solution is filtered and rinsed three times with an

appropriate neutralizing agent. The filter is subsequentiy plated to suitable media such as Trypticase Soy Agar (TSA) and incubated to assess the survival level of the microorganisms. Commonly used neutralization agents are provided in Table 5.2.1-1.
所需的时长到达后，将整个溶液过渡，用适当的中和剂淋洗3次。滤膜盖于适当的培养基上，如胰酶大豆琼脂（TSA），培养，评估微生物的生存水平。常用中和剂见表5.2.1-1.

Alternatively, the solution can be subjected to a serial dilution, with the first dilution using the neutralizing agent and subsequent dilutions using a saline solution. Selected dilutions are then filtered and plated as described above. A pour plate or spread plate method can also be use used with this approach.

也可以将溶液进行逐级稀释，第一次稀释使用中和剂，随后的稀释使用盐水。选择适当的稀释浓度溶液，过滤，如上所述培养。倾倒碟或涂布平板也可以用于此法。

5. A positive control to verify the inoculum concentration for each organism should be prepared as part of each test. For each positive control, the method used in the study should be followed with the exception that the chemical agent should be replaced with saline. Based on the concentration of the inoculums used, appropriate serial dilutions should be made to allow the recovery of between 10 and 300 CFU per plate.
每个测试应制备阳性控制，用于确认每种微生物的接种浓度。每个阳性控制，应与样品制备方法相同，只有化学试剂不要使用。根据所用的接种浓度，需进行适当的稀释等级，使得回收率在10-300CFU/碟。

6. A negative control should also be used to verify that appropriate aseptic technique was employed during the performance of the method. For the negative control, the method used in the study should be followed with the exception that no inoculum should be used. No CFUs should be recovered from the negative control.
在测试中也要使用阴性控制，确认所使用的无菌技术是适当的。阴性控制中，除不接种外，其它操作与样品相同。阴性控制中不应回收到CFU。

7. After the completion of the study, the log reduction achieved against each organism should be determined based on the CFUs present in the inoculum (as determined in the positive controls) and the CFUs recovered from the inoculum exposed to the chemical agent. This level of reduction should be assessed against a set of pre-established criteria to determine if the chemical agent provided the level of reduction required.
在研究完成后，根据接种物中出现的CFU，要确认每个微生物对数减少数量（阳性控制），以及暴露在化学试剂中的接种物回收CFU。该水平的减少数量应与预先建立的标准进行比照，确定该化学试剂是否能提供所需的杀灭水平。

Table 5.2.1-1 Commonly Used Neutralization Agents

Antimicrobial Chemical Agent	Neutralizing Agent
Alcohols	Dilution or polysorbate 80
Sodium hypochlorite	Sodium thiosulfate
Quaternary ammonium compounds	Polysorbate 80 and lecithin
Phenolic compounds	Dilution or polysorbate 80 and lecithin
Hydrogen Peroxide/Peracetic Acid and Hydrogen Peroxide	Catalase

表 5.2.1-1 常用中和剂

杀菌化学试剂	中和剂

乙醇	吐温80或稀释液
次氯酸钠	硫代硫酸钠
季胺盐	吐温80和卵磷脂
酚类	吐温80和卵磷脂或稀释液
过氧化氢/过氧乙酸和过氧化氢	过氧化氢酶

The methods used should be validated to ensure that the neutralizing agent selected does not prevent growth of the various organisms chosen for the studies yet is effective in neutralizing the chemical agent.

所用方法应进行验证，以确保中和剂不会阻止选用于研究的不同微生物的生长，同时又能有效中和化学试剂。

1. To validate the ability of the test organisms to grow in the presence of the neutralizing agent, the test organism (typically at a concentration of <100 microorganisms) and the neutralizing agent should be plated together using a standard pour plate technique and using the same media type that will be used in the studies. The number of CFUs recovered should be comparable with a positive control to which the neutralizing agent is not added.
   为了验证受测微生物在中和剂中的生长能力，受测微生物（一般是取浓度为<100微生物）和中和剂应放置在一起，使用标准倾倒碟技术，使用研究中相同的培养基类型。回收CFU数量应与没有加中和剂的阳性控制相比较。
2. To validate the ability of the neutralizing agent to neutralize the chemical agent, the study method should be performed as written with the exception that the inoculums (typically at a concentration of <100 microorganisms) should be added after the neutralization step has occurred. In the case of a method that uses membrane filtration, the inoculums should be added to the last rinse performed on the membrane before plating. If a pour plate technique is used, the inoculums should be added to the vessel containing the neutralizing and chemical agents. The number of CFUs recovered should be compared to a positive control in which no chemical or neutralizing agent has been added.
   为了验证中和剂中和化学试剂的能力，应按书面的研究方法进行测试，只是接种物（一般浓度为<100微生物）是要在中和步骤完成之后加入。如果使用的是薄膜过滤法，接种物应在最后淋洗完之后在倒碟前加在膜上。如果使用的的倾倒碟，接种物应加在含有中和剂和化学试剂的容器里。回收CFU数量应与没有加化学试剂和中和剂的阳性控制进行比较。

5.2.2 Carrier Surface Studies 载体表面研究

Carrier surface studies are performed to provide a verification of the ability of the antimicrobial chemical agent to reduce the microorganism levels that may be present on the types of material surfaces present within the facility.

载体表面研究是为了证明抗菌化学试剂在设施内所具备的物料类型表面降低微生物水平的能力。

A variety of surfaces that are commonly found in the facility and represent a worst-case porosity or most difficult to clean due to their surface texture should be considered. These may include stainless steel, plastic, plastic bags, glass, vinyl curtains, polycarbonates, and various floor material, such as terrazzo, epoxy, vinyl, and laminate, and wall material, such as painted epoxy and polysubstrates. The number of facility surfaces selected should be based on the criticality of the surface and the risk of such surfaces to harbor contamination that may have an impact on the final product. An example of criticality would be stainless steel. While it is often not found to be the most difficult to clean it is often included due to its close proximity (criticality) to the manufacturing operation.

在设施里通常会有不同的表面，要考虑最差情形或最难清洁的材质。这些材质可能包括不锈钢、塑料、塑料袋、玻璃、乙烯基帘、聚碳酸酯和不同的地面材质，例如，水磨石、环氧树脂、乙烯基物和层压材料，以及墙面材质，例如涂料环氧树脂和聚合基质。设施内表面材质所选择的数量应根据表面的关键程度和这些表面引入可能会对成品有影响的污染的风险程度来决定。关键材质的一个例子就是不锈钢。虽然通常不会发现它是最难清洁的，由于其与生产操作的紧密关系（关键程度），通常会被放在研究考虑中。

The carrier surface used for testing should be made of the material surfaces selected. If coatings, such as clean room paints and epoxy, are selected, they should be coated on non-linting or absorbent surfaces that will not adversely affect test results. It is recommended that the carrier's measurements not exceed 1.5 inches (38 mm) by 1.5 inches (38 mm) so as to avoid false positives during handling of the carrier. Carriers of this size and smaller will fit into a standard test tube without significant manipulations.

用于测试的载体表面应由所选择的材质表面构成。如果所选择的是涂料，例如洁净区涂料和环氧树脂，则应涂布在不起毛或无吸附性的表面上，这样不会对测试结果产生不良影响。建议载体的测量不会超过1.5英寸（38mm）X 1.5英寸（38mm），这样避免在载体处理中发生假阳性。这样尺寸的载体和更小尺寸会适用于标准测试管，不会有重大失误。

However, the size of the carrier will be dependent on the specific method being employed and larger carriers may be used. Prior to use all carriers should be cleaned if needed and properly decontaminated to remove any microorganisms present. Precautions should be taken to ensure that no residual antimicrobial chemical agents are present on the carriers prior to testing. Based on variability within the test methods multiple replicates should be performed, three (3) or more replicates are recommended.

但是，载体的尺寸取决于特定的使用方法，和可能使用的更大载体。在使用之前，所有载体均应进行必要的清洁，进行适当的除污染，以清除任何已有的微生物。要采用预防措施来确保没有残留抗菌化学试剂在测试之前出现在载体上。由于测试方法的差异，应采用多次重复测试，建议平行试验3次。

As with the in-suspension studies, a panel of six to ten microorganisms that include bacteria, yeast, and mold should be used. The organisms chosen should be based on the type of environmental isolates recovered from the facility (environmental isolates are preferred); however, if facility isolates are not available, ATCC cultures (or cultures from other recognized international culture collections) representing facility isolates are acceptable until facility isolates can be obtained.

在悬浮液研究中，使用6-10种微生物，包括细菌、酵母菌、霉菌。所选择的微生物应根据设施里回收的环境中分离物（最好是环境分离物）类型来确定。但是，如果设施分离物无法获得，使用能代表设施分离物的ATCC菌种（或其它认可的国际菌种收藏中心的菌种）也可以接受，直到可以获取设施的分离物。

Presented next are two methods that may be used to complete the studies.

以下给出的是两种方法，都可以用于完成上述研究。

The first method is a total kill method and the second an enumeration method. The total kill method is as follows:

第一法是总杀灭法，第二法为计数法。总杀灭法如下：

1. A fresh culture of each organism is prepared to a known CFU/ml concentration.
   每个微生物新鲜培养制备已知CFU/ml浓度。
2. For each organism, a small volume of the culture is transferred onto the surface of the selected carrier. A sufficient number of microorganisms (10^3-10^5) are placed on the carrier to demonstrate a sufficient reduction of these organisms.
   每个微生物，取一个较小体积至所选择的载体表面。载体表面所含的微生物数量应足够（10^3-10^5），以证明对这些微生物具有足够的杀灭能力。

3. The inoculum applied to the carrier is allowed to thoroughly air dry, after which either the antimicrobial agent is generously applied to the carrier by spraying or wiping or the carrier is submerged within the antimicrobial solution. The chemical agent is then allowed to stay in contact with the carrier for a defined period of time (e.g., five to ten minutes).
将载体上的接种物用空气完全干燥，然后在载体上全面喷洒或涂布抗菌试剂，或将载体浸入杀菌剂溶液。让化学试剂与载体接触指定的时长（例如，5-10分钟）。

4. After being in contact with the chemical agent for the specified time, the carrier is then submerged in a vessel containing a neutralizing agent and appropriate growth medium such as Trypticase Say Broth (TSB) to neutralize the chemical agent.
在与化学试剂接触一定时长后，将载体浸入装有中和剂和适当的的生长培养基如TSB的容器中，中和化学试剂。

5. After a set time, the carrier is placed within a second vessel containing the same growth medium without the neutralizing agent.
过一定时间后，将载体放置在第二个装有相同的培养基但没有中和剂的容器中。

6. Both of the vessels are incubated at the appropriate temperature for a suitable time.
将两个容器在适当的温度培养适当的时长。

7. Using this method, a result of no growth is required in both containers to demonstrate that the required log reduction has been achieved. This level of reduction should be assessed against a set of pre-established criteria to determine if the chemical agent provided the level of reduction required.
使用此方法，两个容器结果均应为无生产，证明达到所要求的对数杀灭效果。此杀灭水平应针对预定的标准进行评估，确定该化学试剂是否能提供所要求的杀灭水平。

8. A positive control to verify the inoculum concentration for each organism should be performed as part of each test. For each positive control, carriers that have been prepared with those to be exposed to the chemical agent should be submerged in a vessel containing a known concentration of saline and gently sonicated or mechanically scrubbed to remove the microorganisms from the carrier. A serial dilution should then be performed from the vessel and plated using the same media type that was used in the test to allow the recovery of between 10 and 100 CFU per plate.
每个微生物均应制备阳性控制，确认接种浓度。每个阳性控制中，要暴露于化学试剂中的载体制备应合并入装有已知浓度盐溶液的容器中，超声或机械方法擦除载体上的微生物。将容器中溶液逐级稀释，使用试验中所用相同的培养基类型铺碟，回收微生物数量应为10-100CFU/碟。

   For example, if TSB is used in the test, TSA should be used for the control.

   例如，如果TSB用于测试，则应使用TSA制作阳性控制。

9. A negative control should also be used to verify that appropriate aseptic technique was conducted during the performance of the method. For the negative control, the method used in the study should be followed with the exception that a sterile carrier should be used. No CFUs should be recovered from the negative control.
在方法实施中，还要制备阴性控制来确认使用了适当的无菌技术。对于阴性控制，应使用研究所用方法，只是要使用无菌的载体。阴性控制中不应观察到回收CFU。

10. After the completion of the study, the log reduction achieved against each organism should be determined based on the CFUs present in the inoculum (as determined in the positive controls).
在研究完成后，对每个微生物的对数杀灭情况应根据接种物中发现的CFU来确定（与阳性控制相同）。

The level of reduction should be assessed against a set of pre-established criteria to determine if the chemical agent provided the level of reduction required.

应根据预定的可接受标准来评估杀灭水平，决定所试验的化学试剂是否达到所需的杀灭水平。

The total kill method should be validated to ensure that the neutralizing agent selected does not prevent growth of the various organisms chosen for the studies yet is effective in neutralizing the chemical agent. The validation can consist of the following:

总杀灭法应进行验证，以确保所选择的中和剂不会阻止选用作研究的不同微生物的生长，但仍能有效中和化学试剂。验证可以如下进行：

1. To validate the ability of the test organisms to grow in the presence of the neutralizing agent, each of the test organisms (typically at a concentration of <100 microorganisms) and the neutralizing agent should be plated together using a standard pour plate technique and using the same media type that will be used in the studies. After appropriate incubation, the number of CFUs recovered should be comparable to a positive control to which the neutralizing agent is not added.
   验证受试微生物在中和剂中的生长能力，使用标准倾倒碟法将每个测试微生物（一般浓度为<100微生物）和中和剂放置在同一碟中，使用研究中所用相同的培养基类型。经过适当的培养，回收CFU数量应与未加中和剂的阳性控制具有可比性。

2. To validate the ability of the neutralizing agent to neutralize the chemical agent as used in the study, the study method should be performed as written with the exception that the inoculums (typically at a concentration of <100 microorganisms) should be added to the vessel containing the neutralizing agent and growth medium after the neutralization step has occurred. Both vessels must show growth.
   在验证中和剂中和化学试剂的能力时，研究方法应按照书面程序实施，只是接种物（一般浓度为<100微生物）要在中和步骤后加到装有中和剂和生长培养基的容器中。两个容器都必须观察到生产情况。

The second method is enumeration, and can be completed as follows:

第二法是计数法，可以按以下步骤实施：

1. The carrier, after having been exposed to the antimicrobial chemical agent as described in method 1, is placed in a vessel containing the neutralizing solution and gently sonicated to remove any organisms.
   将载体按上述1法暴露于抗菌化学试剂中，然后放入装有中和溶液的容器中，超声，去除所有微生物。

2. The entire solution is then filtered, with the filter subsequently plated to a suitable media such as TSA and incubated to assess the survival level of the microorganisms.
   将全部溶液过滤，滤膜随后放入有适当培养基如TSA的碟中，培养，评估微生物存活水平。

   Alternatively, the solution can be subjected to a serial dilution using a saline solution. Selected dilutions are then filtered and plated as described above. A pour plate or spread plate method can also be use used with this approach.

   也可以将溶液用盐水进行逐级稀释。选择稀释液过滤，如上述铺碟。倾倒碟和涂布碟都可用于此法。

3. A positive control and negative control should be performed as described in method 1 above.
   应根据上面第1法所述进行阳性和阴性控制。

8. After the completion of the study, the log reduction achieved against each organism should be determined based on the CFUs present in the inoculum (as determined in the positive controls) and the CFUs recovered from the inoculum exposed to the chemical agent. This level of reduction should be assessed against a set of pre-established criteria to determine if the chemical agent provided the level of reduction required. Recommended acceptance criteria are provided in Table 5.2.2-1.
   在研究完成后，根据接种物中出现的CFU，要确认每个微生物对数减少数量（阳性控制），以及暴露在化学试剂中的接种物回收CFU。该水平的减少数量应与预先建立的标准进行比照，确定该化学试剂

是否能提供所需的杀灭水平。建议的可接受标准列在了表5.2.2-1中。

The method should be validated to ensure that the neutralizing agent selected does not prevent growth of the various organisms chosen for the studies yet is effective in neutralizing the chemical agent. The validation should be performed as described in the first method (total kill) above.

要对方法进行验证来确保所选的中和剂不会阻止用于研究的不同微生物的生长，但仍能有效中和化学试剂。验证应根据上述第一法（总杀灭）所述进行。

Table 5.2.2-1 Recommended Acceptance Criteria 表 5.2.2-1 建议可接受标准

Antimicrobial chemical agent	Organism Type	Suggested Contact Time	Suggested Minimum Reduction
抗菌化学试剂	微生物类型	建议接触时长	建议最小减少量
Sanitizer	Non-spore formers	Max.90 sec	> 1 Log
杀菌剂	非孢子形态	最长90秒	> 1 Log
Disinfectant /Sporicide	Non-spore formers	1-5min	>1 Log
消毒剂/杀孢子剂	非孢子形态	1-5分钟	>1 Log
Disinfectant /sporicide	Mycoplasma	1-5min	>1 Log
消毒剂/杀孢子剂	衣原体	1-5分钟	>1 Log
Sporicide	Mold spores	1-5min	>1 Log
杀孢子剂	霉菌孢子	1-5分钟	>1 Log
Sporicide	Bacterial spores	1-5min	>1 Log
杀孢子剂	细菌孢子	1-5分钟	>1 Log

1. Suggested contact time depends on surface dry times as well as on the room classification the agent is used in, action/alert levels, normal flora, and inoculums. Worker exposure time should also be taken into consideration.
   建议的接触时长取决于表面干燥时长，以及使用试剂的房间级别、行动限/警戒限、常规植物群落和接种物。工人暴露时长也应考虑在其中。
2. Log reduction is defined as the first log being 90%, the second log being 9% and the third log being 0.09% of the original inoculums.
   对数减少量定义为第一次对数为原接种数90%，第二次对数为原接种数9%，第三次对数为原接种数0.09%。

6.0 In-Use Expiration Dating 使用有效期

Sanitizers, disinfectants, and sporicides should be assessed to ensure their performance throughout their assigned in-use period. They should be stored for use no longer than the predefined period as specified by written procedures. The expiration dating provided by the manufacturer relates to the expiration of a closed or "primary" container. Once the container (ready-to-use or concentrate) has been opened, the manufacturer's expiration date is no longer valid for active ingredient potency and sterility.

杀菌剂、消毒剂和杀孢子剂应进行评估以确保其在整个使用有效期内的性能。其存贮时长不应超过书面程序中指定的预定时长。生产商提供的有效期是指在密闭或“原装”容器里。一旦容器打开（直接使用或浓缩液），生产商针对活性成分有效性和无菌性的有效期不再有效。

The important points surrounding in-use expiration relate to the length of time that the solution retains its ability to destroy microorganisms (evaluated in the efficacy testing performed) and, for controlled areas, how long the container and its contents maintain an appropriate bioburden level.

与使用有效期相关的一个重要点是溶液保持其摧毁微生物的能力的时间长度（在进行的效果测试中评估），以及对于受控区域来说，容器及其内容物保持适当的生物负载水平的时间有多长。

This is determined by performing bioburden testing on samples of sanitizer, disinfectant, or sporicide taken from containers (spray bottles, squeeze bottles, etc.) used in the disinfection process at the end of their in-use period.

在使用有效期结束时，对于用于消毒的容器中取出的杀菌剂、消毒剂或杀孢子剂样品进行生物负载试验可以确定上述情况。

7.0 Control of the Environment 环境控制

An effective cleaning and disinfection system starts by limiting the introduction of contamination into the facility by controlling its entry. Stopping as much viable as well as nonviable contamination from entering controlled areas is critical to assuring that the desired environmental conditions are met. If entry of contamination is controlled, the cleaning and disinfection process becomes much less challenging as the quantity of contaminants is reduced.

一个有效的清洁和消毒系统始于通过入口控制减少厂房设施内污染引入。尽可能停止来自入口控制区域的微生物污染和非活性污染对于保证期望的环境条件是关键的。如果入口处的污染被有效控制，因为污染物的量减少了，清洁和消毒过程的挑战性会更低。

On the scale of importance, the control over the introduction of contamination into the environment is the most critical concern in the entire cleaning and disinfection process. This control begins with the cleanliness of items such as components, personnel, carts, tanks, tools, and instruments that are transferred into the facility. A list should be constructed of every item that enters the controlled area, followed by the evaluation of each item, to determine whether or not it can be cleaned and disinfected (or sterilized if needed) effectively. Items that can't be appropriately cleaned and disinfected before entry should be replaced by items that can. The cleaning and disinfection procedures for these items must be formalized. Instituting strict entry controls for all items, including personnel, greatly reduces the level of contaminants entering the controlled areas and as a result reduces the probability of excursions occurring.

在重要性尺度上，对环境内引入污染的控制是整个清洁和消毒过程中最关键的关注点。这种控制开始于转移到该厂房设施内物品如配件，人员，推车，罐，工具和仪器的清洁度。应该构建一个包含每一个进入控制区域的物品的列表，然后对列表中每个物品进行评估以确定它是否能被有效清洁和消毒（必要时灭菌）。不能被适当清洁和消毒的物品进入控制区域前应当用可清洁和消毒的物品代替。这些物品的清洁和消毒程序必须规范化。对包括人员在内的所有项目实行严格控制，极大地降低了进入控制区域的污染物水平，并因此减少了结果发生偏移的可能性。

In addition to controlling the ingress of contamination, concern must also be focused on the proliferation of viable contaminants that are present in the controlled areas. Proliferation of certain types of microorganisms in or on product-contact surfaces such as tanks or bowls, if not cleaned appropriately, can contribute to the level of endotoxins, derived from the cell wall of gram-negative microorganisms, present within a product. Proliferating can also result in a level of bioburden that is difficult to eliminate. Molds, for example, can grow into surfaces or areas that are hard to reach, such as where equipment is attached to the facility's structure, making its elimination much more difficult. For this reason, controlling the environment includes not only limiting the entry of contaminants into the controlled areas of a facility but also limiting the proliferation of these contaminants.

除了控制污染物进入，还必须关注出现在控制区域微生物污染的增殖。如果没有被适当的清洁，在直接接触药品的表面如罐或碗中确定类型革兰氏阴性菌的增殖，其细胞壁会产生大量内毒素并出现在产品中。同时微生物增殖也导致出现难以消除的生物负载水平，例如霉菌，微生物可以伸入难以到达的表面或区域例如设备与厂房设施结构连接的区域，使得其消除变得更加困难。因此，环境控制不仅包括限制污染物进入厂方设施控制区域，同样包括限制微生物污染增殖。

There are three high-risk time periods when the entry of contamination can impact operations:

下面是污染物进入影响操作的三个高风险时间段：

1. After cleaning and disinfection and before manufacturing begins, production personnel and the components enter the area and potentially shed particulates and microbes. This is a critical time period as setup occurs after disinfection is complete.
   清洁和消毒之后开始生产前，生产人员和配件进入该区域可能脱落微粒和微生物。消毒完成后安装时是一个关键时间段。
2. During manufacturing interventions, personnel may contaminate disinfected or sterilized surfaces through inappropriate clean room behavior and poor aseptic techniques. Shedding of particulates, microbes, and fibers onto manufacturing surfaces can cause contamination.
   在制造过程的干预措施中，人员不恰当的洁净室行为和较差的无菌操作技术可能污染消毒或灭菌后的表面。脱落到制造区域表面的颗粒，微生物和纤维造成污染。
3. After manufacturing and before cleaning and disinfection, personnel must remain conscious of the impact that their aseptic behavior and practices may have on the cleanliness of the environment.
   制造完成后在清洗和消毒之前，工作人员必须意识到他们的无菌操作行为和做法可能对环境的洁净度产生影响。

Areas of concern for maintaining low levels of contamination entering manufacturing areas include but are not limited to the following:

为保持进入生产制造区域的污染处于低水平，关注区域包括但不限于以下内容：

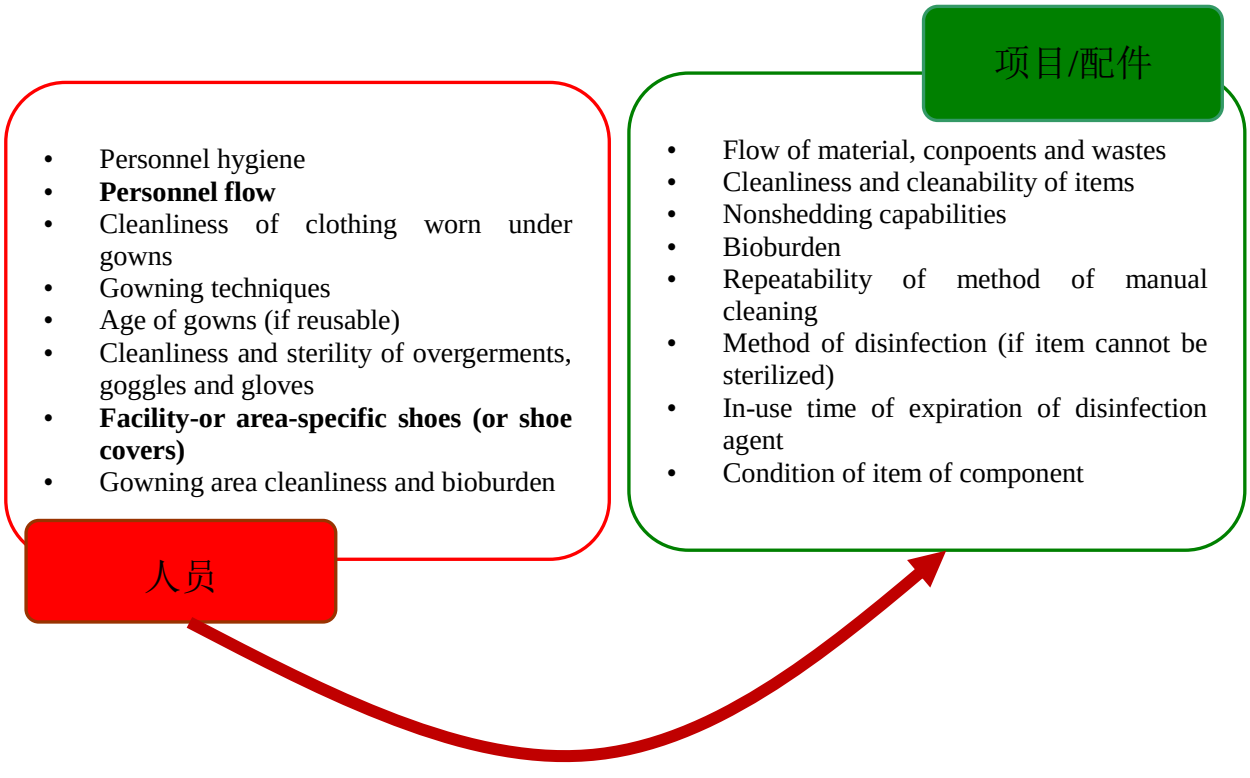

Figure 7.0-1 Considerations to Maintain Low Levels of Contamination

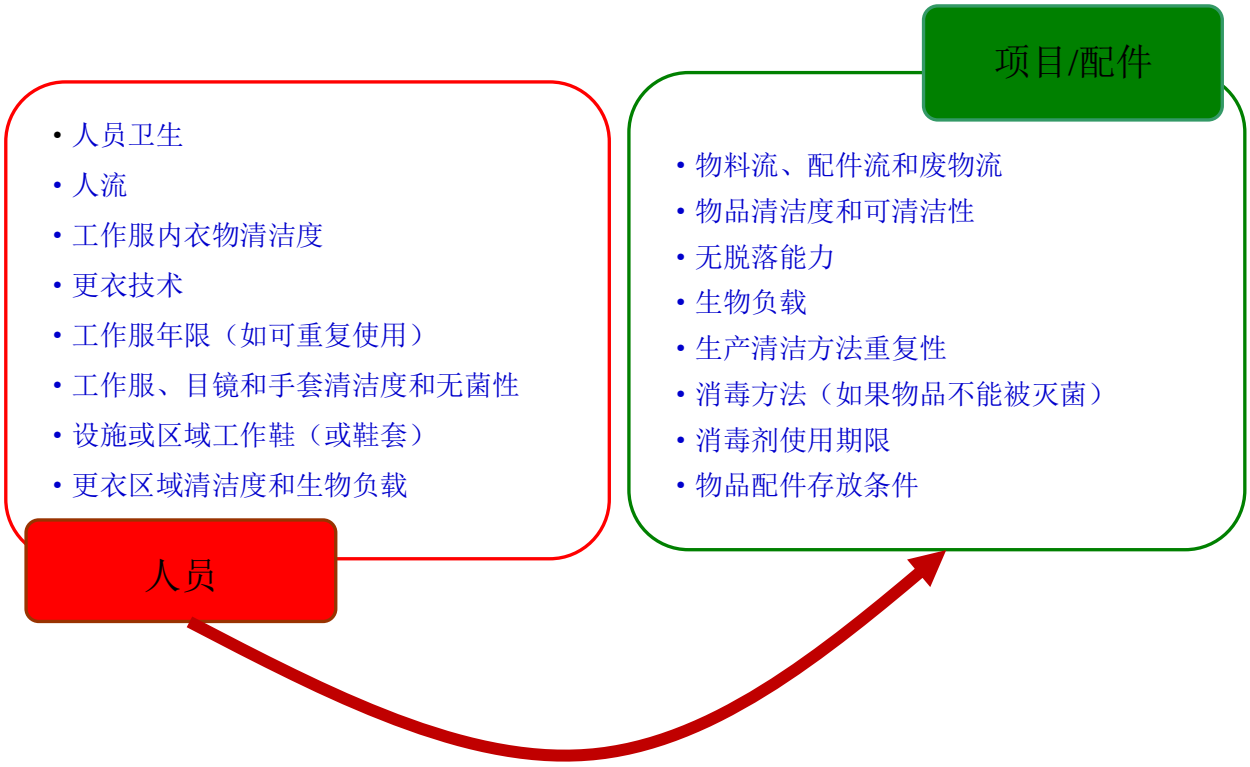

图7.0-1保持低水平污染的关注点

7.1 Introduction of Clean Room Manufacturing Supplies 洁净室生产辅助用品介绍

The design of the facility and the procedures in place must assure the prevention of contamination from the flow of components, drug products, containers, closures, labeling, in-process materials, and products through the building or buildings.

厂房设施和在位程序的设计必须能够阻止组件，药物制品，容器，密封，贴签，在加工材料和产品通过一个或多个建筑物所带来的污染。

As emphasized in the U.S. FDA *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practices:*

正如FDA工艺指南：采用无菌工艺生产的无菌药品—cGMP中强调的：

> *It is critical to adequately control material (e.g., in-process supplies, equipment, utensils) as it transfers from lesser to higher classified clean areas to prevent the influx of contaminants. For example, written procedures should address how materials are to be introduced into the aseptic processing room to ensure that room conditions remain uncompromised. In this regard, materials should be disinfected according to appropriate procedures or, when used in critical areas, rendered sterile by a suitable method. (4)*
>
> 对低级别洁净区向高级别洁净区转移材料（如，在线辅助材料，设备，器具）的适当控制对于阻止污染物的流动是关键的。例如，应用书面程序解决如何在确保室内环境保持不被破坏的前提下将材料引入到无菌工艺房间。在这方面，材料应能依据适当的程序进行消毒，或者当材料被用于关键区域时能依靠一个合适的方法实现无菌。（4）

Good facility design makes the process of item introduction easier and more consistent. Sterilizers, vaporized phased hydrogen peroxide (VPHP) chambers, airlocks, and pass-through ports all share a common design element,

such that one side is designated "clean" and the other side is designated "dirty."

好的厂房设施设计使得产品引进变得更简单稳定。灭菌柜，汽化过氧化氢灭菌室（VPHP），气锁间，通行端口都有一个通用的设计元素，即一侧被定义为“清洁”的，而另一侧被定义为“脏”的。

The following sections will discuss introduction of items into aseptic processing areas (APA) of the facility. Clean room manufacturing supplies include a broad range of items, such as:

接下来的章节将讨论厂房设施无菌工艺区域（APA）内物品的引入。洁净室生产辅助物品包括一个宽范围例如：

- Mechanic's tools
- 维修人员的工具
- Carts
- 推车
- Production supplies
- 生产辅助物品
- Handling implements
- 操作器具
- Environmental monitoring supplies
- 环境监测设备
- Wipers
- 刮水器
- Antimicrobial chemical agents
- 抗微生物化学物质
- Filling equipment components
- 灌装设备组件
- Non-product-contact components
- 非直接接触产品组件
- Markers and pens
- 记录和笔
- Electronic equipment (e.g., meters and particle counters)
- 电子设备（例如仪表和粒子计数器）

Items entering the APA should be exposed to the highest level of decontamination that the material can withstand. If an item can be physically sterilized, it must be. The two most widely used methods of sterilizing items entering the APA are autoclaving and gamma irradiation. For items that are gamma irradiated, a number of wraps, barriers, or layers that can be removed when passing to a more stringent grade are normally used. This concept of using multiple outer layers can also be applied to items that are autoclaved, if the autoclave does not directly open into the APA. Items that cannot withstand the temperatures of autoclaving or rigors of irradiation should be introduced using a decontamination process (VPHP, for example) within a pass-through or a manual disinfection (i.e., spraying or wiping) using a sporicidal agent. Ultraviolet (UV) pass-through systems can also be used to reduce

bioburden of items but should not be considered a sterilization method.

进入APA（无菌工艺区域）的物品应暴露于其材料能耐受的最苛刻污染消除水平。可以采用物理方法灭菌的物品必须进行物理灭菌。物品进入APA应用最广的两个灭菌方法是湿热灭菌和γ-射线照射灭菌。多层包裹，有屏障的物品以及带有多层可去除包装的物品被传递到更高级别时通常使用γ-射线照射灭菌。如果湿热灭菌器不直接开向APA里面，使用多层外包的理念也同样适用于湿热灭菌。不能耐受湿热灭菌温度或严酷辐照的物品传递时应使用净化工艺（例如VPHP）或使用杀孢子剂进行全面消毒（喷涂或擦拭）。紫外线（UV）传递系统同样可用于降低物品生物负载，但不应该被认为是一种灭菌方法。

When using an automated decontamination chamber, each item must be validated using the chosen cycle. Additionally, care should be taken during arrangement of items to maximize the surface area exposed to the agent. If, for some reason, an item is incapable of being disinfected before entering the clean room, it should not be introduced and a suitable alternative should be found.

使用自动化净化室时，每种物品都必须定期进行验证。另外物品摆放时应注意使物品暴露最大表面区域。如果由于某种原因，一个物品在进入洁净室之前不能被消毒，该物品不应被引入洁净区，应寻找合适的物品代替。

Personnel should not carry items through the gowning room.

人员不应携带物品穿越更衣室。

7.1.1 Types of Clean Room Disinfecting Agents 洁净室消毒剂种类

As described earlier, antimicrobial chemical agents can be classified into three categories: sanitizers, disinfectants, and sporicides. Listed here are the types of agents that are commonly associated with each category.

如前所述，抗微生物化学试剂可分为三类：杀菌剂，消毒剂和杀孢子剂。这里列出的是通常与每个类别相关联的试剂类型。

1. Sanitizers: Alcohols (namely, isopropanol and ethanol) are chemicals agents that should be employed when disinfecting items that have been brought into the APA as they are quick to evaporate and leave minimal residue. Isopropyl alcohol (IPA) 70% should be used in favor of ethanol (EtOH) 70%, unless material interactions prohibit, because the bactericidal action of IPA is considered slightly greater than that of ethyl alcohol. While alcohols have relatively good biocidal activity on vegetative cells, their rapid rate of evaporation significandy reduces their effectiveness.Alcohols have no effect on spores.

   杀菌剂：由于蒸发快、残留低的特点，消毒已被带入APA的物品时应使用醇类（即异丙醇和乙醇）化学试剂。除非与材料存在相容性问题，应使用70％异丙醇（IPA）代替70％乙醇（EtOH），因为异丙醇的杀菌作用被认为比乙醇稍大。虽然醇类对活细胞具有相对较好的杀菌活性，但醇类的快速挥发显著降低了其效力。醇类杀菌剂对孢子无效。

2. Disinfectants: Phenols and quaternary ammonia compounds provide broad-spectrum kill of vegetative cells. These chemicals characteristically leave residues on surfaces. Immediately following their use, such residues should be removed, for example, via IPA wipe-down.

   消毒剂：酚类和季铵化合物对活细胞具有广谱杀菌活性。这些化学物质典型特征会带来表面残留。紧随它们的使用应清除该部分残留，例如通过异丙醇擦拭清除。

3. Sporicides: Sodium hypochlorite (bleach) and hydrogen peroxide/peracetic acid compounds are widely used sporicidal agents. Hydrogen peroxide can also be used (normally at 6%) to provide activity against molds and some spore-forming organisms. Peroxides are more active than alcohols and break down into water and oxygen, leaving no residue. Sporicidal chemicals should be employed when a disinfecting procedure requires the reduction of spore-forming organisms. Unfortunately, with the exception of

hydrogen peroxide these chemicals leave some amount of residue.

杀孢子剂：次氯酸钠（漂白剂）和过氧化氢/过氧乙酸化合物是广泛使用的杀孢子剂。过氧化氢也可用于（通常在6%浓度）提供对霉菌和一些孢子形式微生物提供抗菌活性。过氧化物比醇类抗菌活性更高，分解后形成水和氧气，不产生留残。当消毒程序要求清除孢子类微生物时应采用化学杀孢子剂。不幸的是，除过氧化氢外这些化学品均有一定残留。

7.1.2 Introduction of Tanks, Vessels, Carts, and Equipment into the APA 进入无菌操作区域的罐、容器、推车和设备介绍

The transfer of equipment into an aseptic system can result in the introduction of contamination and, therefore, must be addressed accordingly. Ideally, this decontamination would be done via an autoclave or VPHP chamber; however, it is commonly performed manually.

设备转移到无菌系统内可导致污染引入，因此必须进行相应的处理。理想条件下去除污染将通过湿热灭菌柜或VPHP室进行；然而它通常被手动执行。

During the disinfecting process, special attention should be given to cleaning and disinfecting the wheels of carts and mobile equipment. In the manual cleaning and disinfection of cart wheels increased contact time and mechanical wiping techniques should be employed. Wiping with a particulate free, non-shedding wipe to clean to wheel should be accomplished first followed by appropriate disinfectant application on the wheels that assures an appropriate and validated contact (dry) time.Where a VPHP or other type of decontamination chamber is used, the wheels should be wiped down with a cleaning agent and subsequently sprayed with an antimicrobial chemical agent prior to entering the chamber.

在消毒过程中，应特别注意对推车轮子和移动设备进行清洁和消毒。在手动清洁和消毒推车车轮时应增加接触时间并采用物理擦拭技术。清洁轮子时首先应采用无脱落物、无颗粒释放的抹布擦拭，其次是在轮子上应用适当的消毒剂确保适当的经验证的接触（干燥）时间。在使用VPHP或其它类型的去除污染净化室时，在进入净化室之前应当用清洁剂擦拭轮子，然后喷洒抗微生物试剂。

7.1.3 Introduction of Cleaning Supplies and Equipment into the APA **进入无菌操作区域的清洁辅助用品和设备介绍**

Cleaning supplies and cleaning equipment also represent potential bioburden sources to the controlled environment. Therefore, prior sterilization or disinfection of these items should be considered a standard practice.

对于受控环境，清洁用品和清洁设备同样代表了潜在的微生物负载。因此，这些物品在灭菌或消毒之前应考虑采用一个标准规范。

Cleaning equipment such as buckets, mops, mop handles, mop heads, sprayers, wipes, and extensions should be thoroughly cleaned and rendered sterile prior to use in the Grade A (ISO 5) and adjacent Grade B (ISO5/6) areas. Sterilization of cleaning equipment can be accomplished through steam sterilization or the use of sterile one-time-use disposable systems, among other methods.

清洁设备，如桶，拖把，拖把手柄，拖把头，喷雾器，抹布，和延长器，在A级区（ISO5）和相邻的B级区（ISO5/6）使用之前应彻底清洁并灭菌。清洁设备灭菌可以通过蒸汽灭菌或使用一次性无菌系统等其他方法完成。

Sanitizers, disinfectants, and sporicides can harbor resistant microorganisms in the solution and, therefore, must be addressed to reduce or eliminate such bioburden. The removal of bioburden from solutions prior to use in the Grade A (ISO 5), adjacent Grade B (ISO 5/6), and adjacent Grade C (ISO 7) areas are critical to assure that such contaminants are not transferred to the controlled areas. Microorganisms (normally spores) residing in sanitizers, disinfectants, and sporicides represent a breach in control during a critical time of cleaning prior to manufacturing.

If a bioburden load is permitted to enter through the cleaning process, there is no mechanism in place that will remove their presence before manufacturing.

杀菌剂，消毒剂和杀孢子剂溶液中会携带耐药微生物，因此，必须通过减少或消除这种生物负载解决。在A级（ISO5）区域、相邻的B级区域（ISO5/6）以及相邻的C级区域（ISO7）使用前，去除微生物负载对于防止污染转移至控制区域是关键的。存在于杀菌剂，消毒剂和杀孢子剂中的微生物（通常是孢子形式）在关键的生产前清洁期间代表一个控制缺口。如果生物负载通过清洁过程被引入，生产之前没有在位的机制能去除其存在。

To ensure sanitizers, disinfectants, and sporicides do not represent a source of contamination, they should be sterile-filtered or sterilized before use in Grade A (ISO 5) and adjacent Grade B (ISO 5 / 6) areas.

为确保杀菌剂，消毒剂和杀孢子剂不成为污染源，在A级区（ISO5）和相邻的B级（ISO5/6）区使用前应过滤除菌或灭菌。

A firm should validate the sterilization or sterile filtration process or require appropriate proof of sterilization from outside vendors before use of the solutions in these areas. Examples of approaches that may be used to ensure that the sanitizers, disinfectants, and sporicides are not the source of contamination are listed below:

在这些区域使用前上述试剂前，企业应验证灭菌工艺或无菌过滤工艺，或要求外部供应商提供无菌的适当证明。下面列举的是为确保杀菌剂，消毒剂和杀孢子剂不成为污染源可采取的措施举例：

- ·Aseptic filtration at 0.2 μ, of the final use dilution from outside the Grade A/B (ISO 5/6) area directly into presterilized holding containers or vessels located in a Grade A/B (ISO 5/6) area. If filtration into presterilized holding containers or vessels is conducted outside of the Grade A/B (ISO 5/6) area, then routine bioburden sampling should be conducted prior to its entry into the Grade A/B (ISO 5/6) area.
- 从A/ B级（ISO5/6）之外的最终使用稀释区直接经0.2μ无菌过滤至预先灭菌的暂存容器或位于A/ B区（ISO5/6）内的容器中。
- ·Mixing of a solution in the Grade A (ISO 5) and adjacent Grade B (ISO 5/6) areas using a presterilized unit dose container where the solution has been certified as sterile. Such unit dose containers should be mixed with sterile USP Water for Injection.
- 在A级区（ISO5）和相邻的B级区（ISO5/6）使用预先灭菌的单位剂量容器直接混合配制，配制的样品已经被确认处于无菌状态。该单位剂量样品的混合应使用符合USP标准的无菌注射用水。
- ·Purchase of a ready-to-use or ready-to-mix (where two solutions are packaged together such that they can be mixed) sterile solution from an outside vendor that is delivered with appropriate documentation confirming its sterility.
- 从外部供应商采购已提供适当文件证明其无菌性的可直接使用或直接混合（两种溶液被包装在一起，使得前可以混合）的无菌溶液。
- ·Sterilization of the mixed solution in an autoclave (if acceptable based on the composition of the solution).
- 在湿热灭菌柜中对混合溶液进行灭菌（基于溶液组分的接受能力）。

Containers that aspirate air into the container, such as squeeze bottles, trigger sprayers, and bulk containers that are opened and closed, should be used for a limited time as defined in written standard operating procedures. As an illustration of the potential problems, 70% IPA bottles that aspirate have been known to harbor mold cells that may have been introduced into the container from the clean room environment. Nonaspirating containers neither

introduce contamination to the master reservoir nor allow active ingredients to escape, which would lessen their effectiveness. Nonaspirating containers may be used until the validated expiration period defined for the product.

能够吸入空气的容器如挤瓶，触发喷雾器，以及需打开和关闭的散装容器，应在书面SOP所定义的期限内使用。作为潜在问题的例证，70％异丙醇（IPA）吸瓶已经被发现带有可能被引入洁净室环境容器中的霉菌细胞。非吸气容器既不会将污染引入贮液，也没有让活性成分逸失，活性成分逸失将降低其有效性。非吸气容器可以一直使用直到该产品定义的验证有效期。

A sanitizer, disinfectant, or sporicide solution in an open container that has been used in the Grade A (ISO 5) area can subsequently be used in the adjacent Grade B (ISO 5/6) and Grade C (ISO 7) areas, in that order. However, extensively used solutions (dirtied solutions) can compromise the cleaning operation and the antimicrobial effectiveness of the solution. Sterile solutions used in the Grade A (ISO 5) area and subsequently used in a lower classification cannot be used in a Grade A (ISO 5) area again, unless the contents of the solution are kept underpressure, so as not to return contamination to the vessel. Consideration should be given to establishing limits for the total area covered for each batch of solution. Where open bucket systems are used the contents should be discarded upon completion of the cleaning operation as stated above.

开放容器内的杀菌剂,消毒剂或杀孢子剂溶液在A级区（ISO5）使用之后可以按顺序在相邻的B级区（ISO5/6）和C级（ISO7）区被使用。但是，溶液的广泛使用（脏的溶液）会危及清洁操作及该溶液的抗微生物效力。在A级区（ISO5）使用的无菌溶液可以在较低的级别使用但不能再次用于A级（ISO5）区域，除非该溶液的容器保持负压，不会导致污染返回到容器中。应考虑建立每批溶液总覆盖面积的限制。当使用如上所述散装系统时，清洁操作完成后应丢弃其容器。

7.1.4 Introduction of Components into the APA 进入无菌操作区域的组件介绍

The term "components" refers to items that are used directly in the manufacturing process. Stoppers, plungers, vials, and cartridges are some of the most common components. Depyrogenation and sterilization are required for components that come into direct contact with the sterile product (e.g., vials and stoppers) within the aseptic processing area (1). A validated sterilization process must be used for components entering the APA, and this sterility must be maintained after components have entered the APA through integration into the final product. Depyrogenation and sterilization can be achieved with dry heat or through a validated washing and sterilization process. If components are sterilized outside of the APA, multiple outer wraps, layers, or barriers should be used to allow for appropriate disinfection before entering the Grade A (ISO 5) environment for integration into the final product.

术语“组件”是指在制造过程中直接使用的物品。塞子，冲头，小瓶和墨盒是一些最常用的组件。在无菌操作区域内直接接触无菌药品（例如，小瓶和塞子）的组件要求除热原和灭菌。进入无菌操作区域的组件必须使用经验证的灭菌工艺，并且应维持这种无菌状态直到已进入无菌操作区域的组件被整合到最终产品中。除热原和灭菌可以通过干热或经验证的清洗灭菌工艺实现。如果组件在无菌操作区域之外灭菌，应使用多层包装以允许组件在进入A级区（ISO5） 环境整合到最终产品之前进行适当的消毒。

Sterilization and depyrogenation of product-contact surfaces are of the utmost concern. The appropriate methods to accomplish this are outside of the scope of this document. For additional information see PDA *Technical Report No. 3 (Revised 2013): Validation of Dry Heat Processes Used for Depyrogenation and Sterilization (12).*

与产品直接接触的表面的灭菌和除热源都是极为关注的问题。完成该问题的适当方法在本文件的范围之外。更多有关信息参照PDA*技术报告No.3（2013年修订）：用于除热原和灭菌的干热灭菌工艺验证（12）*。

7.2 Environmental Monitoring Data Analysis 环境监测数据分析

Environmental monitoring data demonstrates the effectiveness of the microbial contamination control system, which includes the cleaning and disinfection program. The actual genus and species of organisms found; the

numbers; and the distribution within the facility compared to the trending history, indicate if the data are consistent with historical area performance or if there has been a shift in control. The data attain a predictable profile, and typical organisms have been isolated when the facility is considered in control. The most common isolates are typically those from people, with fewer isolates from air or soil and water or liquid sources. Data may be analyzed in a number of ways, such as by area, by product, by process, or by organism type. Formal, documented analysis of all microbial environmental data trends should be performed periodically. Evaluating the effectiveness of control, cleaning, and disinfection programs and the adequacy of the current alert and action levels should be performed at least annually. The analysis should include the types and numbers of organisms found and their locations. Following the analysis, this information should be reported to site management, then reviewed and documented by quality management. In addition to the long-term reporting, short-term analysis should also be performed to determine if the areas are in control.

环境监测数据包括清洁和消毒程序代表微生物污染控制系统的有效性。厂房设施内发现的微生物种属、数量和分布与历史趋势相比较，表明该数据与历史数据表现一致或有受控的偏移。当监测数据达到预期的轮廓且典型的菌株已经被分离时，该厂房设施被认为是受控的。最常见的菌株通常来源于人，少量菌株来源于空气或土壤以及水或其他液体。监测数据可以按照多种方式分析，例如按区域分析，按产品分析，按工艺分析或按菌株的类型分析。所有微生物环境数据趋势分析应定期记录完成。至少每年评估控制，清洁，消毒程序有效性以及现行的警戒限行动限是否充分。分析应包括发现的微生物的种类，数量和它们的位置。分析之后这些信息应该报告给现场主管，然后由质量主管审查记录。除了长期报告，短期分析也应被执行以确认区域受控。

Any change from the normal condition creates a signal, usually referred to as an adverse trend or excursion.An adverse trend will usually require some type of action. Actions can vary from simple notifications for heightened awareness when alert levels are reached or atypical organisms are isolated, to special cleaning and disinfection of the area, to a full investigation when action levels are exceeded on multiple occasions or at multiple monitoring sites.

来自正常状态的任何改变产生的信号，通常被称为是一个不良趋势或偏移。不良趋势通常要求采取某种类型的行动。当结果达到警戒限或分离到非典型菌株时，所采取的行动可以在简单的通知提高警觉到对相关区域进行特别的清洗和消毒之间变化，当在多个场合或多个监测点监测结果达到行动限时进行一个全面的调查。

Adverse data trends should be evaluated to establish the microorganism source (personnel related, from the air or soil, or related to water or liquid sources), if organisms are different from ones previously encountered or if they were found at locations where they would not be expected. Organism specific corrective actions could include increased use of sporicides or further control mechanisms if organisms producing spores or fungi are found. The reaction to data shifts, signals, or trends should be proportional to the risks imposed by the sampling location and the potential for the contamination to spread. All aspects related to control should be considered and methodically evaluated as the possible cause of the deviation. Return to sustained acceptable data is the long-term measure of success.

应对不良数据趋势进行评估以确定微生物来源（相关人员，空气或土壤，或相关的水或液体），是否分离得到未曾出现的菌株或在预期不会出现到的位置被发现。如果菌株产生孢子或发现真菌，具体的纠正措施可能包括增加杀孢子剂使用或进一步的控制机制。对数据、信号的偏移或趋势的反映应与由采样位置或污染扩散带来的风险成比例。应考虑控制相关的所有方面并有序评价出现偏差的可能性，达成成功的长期措施是返回持续的可接受数据。

For example, the recovery of vegetative organisms above action levels would signal the possible need for temporarily increased control and/or increased disinfection.However,detection of spore-forming organisms above

the action level could indicate the need for an immediate response using sporicidal agents. The investigation into a data shift, signal, or trend may indicate that the disinfection program needs to be adjusted.

例如，有生长能力的菌株恢复至超过行动限表明暂时增强控制和/或消毒的可能需求。然而，检测到超过行动限的孢子形式微生物表明需立即使用杀孢子剂。对一组数据、信号偏移或趋势的调查可能表明消毒程序需要调整。

Additional information on environmental monitoring can be found in PDA *Technical Report No. 13 (Revised 2014): Fundamentals of an Environmental Monitoring Program (13).*

环境监测的更多信息可以在PDA技术报告No.13（2014年版）：环境监测程序基础（13）中找到。

7.3 Attaining and Selecting Environmental Isolates 环境菌株的发现和选择

Recoveries of microorganisms from environmental monitoring samples should be identified to genus and species level when exceeding alert or action levels, and periodically when limits are not exceeded.Organism identifications should be evaluated to determine the most frequently occurring organisms.Representative organisms should be preserved and included in the panel of organisms in efficacy testing of antimicrobial chemical agents used in the facility.

当超过警戒限或行动限时，环境监测样品中回收的微生物应鉴别种属，不超过限度时定期回顾。菌株鉴别应通过评估以确定最频繁出现的菌株。典型的菌株应予以保留并列入在厂房设施中使用的抗菌化学物质效力测试生物板。

8.0 In-Situ Field Studies 现场领域研究

The true test of the effectiveness of a cleaning and disinfection program is the monitoring data collected from the manufacturing area. Evaluation of the in-situ data being generated from a robust environmental monitoring program will verify that the program is capable of attaining and maintaining a level of cleanliness that minimizes the probability of contamination of the manufacturing process by the environment.

在生产制造区域收集的监控数据是对清洁和消毒程序有效性的实际测试。对从一个稳健的环境监测程序获得的现场数据的评估，将验证该程序能达到和维持一个洁净水平，使制造工艺可能的环境污染最小化。

These in-situ data may include the following:

这些现场数据可能包括以下内容：

- Nonviable (total particulate data)
- 非活物质（总颗粒数据）
- Viable data for surfaces and ambient air
- 表面和周围空气的微生物数据
- Personnel-monitoring data
- 人员监控数据
- Microbial identification of representative isolates from the environment
- 环境中分离微生物的种属鉴别
- Residual testing of surfaces
- 表面残留检测
- Product quality (in-process bioburden and sterility testing)
- 产品质量（在线生物负载和无菌检测）

Two approaches to conducting in-situ monitoring are commonly used.

进行现场监控的两种途径被广泛使用。

8.1 Environmental Monitoring Before and After the Start-up of a Facility or Area 厂房设施或区域启用前后的环境监控

In this approach, several scenarios may be applicable. They include the opening of a new area of a facility, area shutdown due to adverse events, an area that has undergone significant modifications with no special constraints to personnel or material entry, or an area that has be left idle for a significant period of time with no special constraints to personnel or material entry. Facilities should strongly consider having special start-up cleaning and disinfection programs in place following shutdowns or when significant construction has been performed.

在这种方法中有几种情况可能是适用的。它们包括厂房设施中新区域的启动或由于不良事件关闭区域，或经过显著变更但对人员或物料进入没有特殊限制的区域，或者已被闲置一段时间且对人员或物料进入没有特殊限制的区域。厂房设施在关闭或执行显著建设后应强烈考虑制定专门的启用时在位清洁和消毒程序。

Many programs follow viable monitoring after each step of a start-up program to document the effectiveness of each stage of the cleaning and disinfection program, with this approach:

许多程序在一个启用程序的每一步完成后进行微生物监测以记录清洁和消毒程序每一步的有效性，采取这种方式：

- An initial cleaning is performed. An initial cleaning entails the removal of soil using a broom or vacuum; for example, cleaning the facility after completion of construction to prepare the facility before starting the formal cleaning process.
- 执行初始清洗。初始清洗需要用扫帚或真空去除灰尘;例如，在厂房设施建设完工后正式清洁工艺之前对厂房设施进行清洁。
- Increased viable monitoring of air and surfaces is performed to attain baseline data for comparison with data acquired after the cleaning and disinfection processes are performed. Nonviable air monitoring may also be performed.
- 增加空气和表面的微生物监测以获得基线数据，用于与清洁消毒程序执行后获得的数据进行比较。非活物质空气监测也应执行。
- Facility cleaning and disinfection are performed.
- 执行厂房设施清洁和消毒。
- After the cleaning and disinfection are complete and surfaces are dry, the increased viable monitoring of surfaces should be repeated. Nonviable air monitoring should also be performed. Non-viable air monitoring provides date related to the cleaning process overall and the resulting particulate level present.
- 在清洁和消毒完成且表面干燥之后，表面增加的微生物监测应该被重复，非活物质空气监测也应执行。非活物质空气监测提供与清洁工艺整体和得出当前颗粒水平相关的数据。

After the cleaning and disinfection program has been implemented, the monitoring results from before and after the implementation are analyzed. The expectations from a robust cleaning and disinfection program would be the reduction of the level of viable and nonviable counts and minimization of any spore-forming or mold contaminants initially found. If the results do not demonstrate an acceptable level of reduction, the cleaning and disinfection program should be reviewed and modified where appropriate.

清洁和消毒程序实施后，分析实施前后的监测结果。来自一个完善的清洁和消毒程序的预期是减少微生物和非活物质数量并使任何孢子形式微生物或初期发现的霉菌最小化。如果结果没有表现出可接受的减少，清洁和消毒程序应被重审并修改至合适。

8.2 Environmental Monitoring Before and After Cleaning and Disinfection During Routine Operation 日常操作期间清洁和消毒前后的环境监控

In this approach, a facility is in routine manufacturing operation to evaluate the effectiveness of the cleaning and disinfection program the follow approach is taken:

用这种方法，厂房设施在日常生产操作中评价采取下列措施的清洁和消毒程序的有效性：

- Increased viable surface and air monitoring is performed after operations have occurred and just before cleaning and disinfection take place. Nonviable air monitoring should also be performed.
- 在操作完成后清洁和消毒前增加表面和空气微生物监测，非活物质空气监测也应执行。
- Cleaning and disinfection are performed.
- 进行清洁和消毒。
- Increased monitoring is performed again after cleaning and disinfection.
- 清洁和消毒后再次增加监测。

The data gathered before and after implementation of the cleaning and disinfection program is then analyzed. The expectations from a robust cleaning and disinfection program would be the reduction of the level of viable and nonviable counts and minimization of any spore-forming or mold contaminants initially found. If the results do not demonstrate an acceptable level of reduction, the cleaning and disinfection program should be reviewed and modified where appropriate.

然后进行分析清洁和消毒程序实施前后获得的数据。来自一个完善的清洁和消毒程序的预期是减少微生物和非活物质数量并使任何孢子形式微生物或初期发现的霉菌最小化。如果结果没有表现出可接受的减少，清洁和消毒程序应被重审并修改至合适。

Additional information on environmental monitoring can be found in PDA *Technical Report No. 13 (Revised 2014): Fundamentals of an Environmental Monitoring Program (13).*

环境监测的更多信息可以在PDA*技术报告No.13（2014年修订）：环境监测程序的基础（13）*中找到。

9.0 Cleaning And Disinfection 清洁和消毒

Cleaning is a critical step in the cleaning and disinfection process because the buildup of antimicrobial chemical agent residues, product residues, particulates, and other contaminants can inhibit an antimicrobial chemical agent's efficacy. Cleaning requires a nondestructive mechanical action that loosens and removes contaminants from the area or equipment surface. Procedurally, a cleaning agent is applied via a nondestructive mechanical action method. Contaminants and residues are loosened and rinsed from the surface and removed with a squeegee or dry cloth. By lessening the level of particulates, microbes, and residues on the surface, cleaning prepares the surfaces for disinfection and the disinfection efforts become more effective because of the following:

因为化学抗菌试剂的残留，产品的残留，粒子以及其他污染物的累积会抑制化学抗菌剂的效力，因此，清洁是清洁与消毒中非常重要的步骤。清洁是一种非破坏性的依靠机械的运动来减少或去除区域和设备表面的污染物。顺序使用清洁剂是一种非破坏的机械运动方法。污染物和残留物质从表面减少或擦下来后，用橡胶滚轴或干毛巾移除。清洁步骤通过减少表面的粒子，微生物以及残留为消毒做好准备，使得消毒更加有效，理由如下：

- There are fewer organisms to destroy, as most have been removed from the area.
- 由于大部分微生物已经从该区域移除，只留下很少的为微生物需要破坏。
- Obstructions blocking the chemical agent from contacting the organism are minimized.
- 阻止化学试剂与微生物接触的障碍物变少。
- Chemical interference that would reduce the stability and effectiveness of the active agents is removed.
- 降低活性试剂稳定性和有效性的化学剂的阻碍力已经被消除。
- Lessening of residual that can interfere with future disinfection and/or can dry or flake off and release to the environment.
- 干扰后期消毒的残留物和/或干燥或剥落后释放到环境中的残留物变少。

An antimicrobial chemical agent's efficacy requires the saturation and penetration of the organism's cell wall by the chemical agent for a set amount of time depending on the agent used. Disinfection efficacy depends on a number of factors, including the active ingredient used, air and surface temperatures, saturation and penetration of the cell wall, wetted (contact) time, surface material substrate and bioburden of the surface, existent soil load, concentration of the chemical agent, and pH. Provided the appropriate chemical agent is used, the key to disinfection in the clean room is keeping the surface wetted for a sufficient period of time for the chemical to accomplish its mode of action. Drying time is a variable that must be carefully evaluated as the movement of air in clean rooms (especially in areas where unidirectional airflow is present) tends to dry surfaces quickly.

根据使用试剂的不同，需要试剂饱和并穿透在微生物细胞壁并稳定一段时间，才能使化学抗菌试剂发生效用。灭菌的有效性取决于诸多因素，包括所用的活用成分、空气和表面温度、细胞壁的饱和和穿透、润湿（接触）时长、表面材料基质和表面的生物负载、滋养成分、化学试剂的浓度以及pH值。如果使用了适当的化学试剂，洁净间里灭菌的关键就是保持表面润湿足够时长，使得化学试剂能完成其灭菌模式。干燥时长是一个变数，必须小心评估，因为洁净间内的空气流动（尤其是非直流气流存在时），最好尽快让被灭菌的表面干燥。

The effect of the buildup of residues, particulates, and possibly microbes is also affected by the surface itself.

Irregular or porous surfaces trap residues and other contaminants and make the surface more difficult to clean and disinfect. Development of appropriate cleaning systems is critical to successfully preparing a surface for disinfection. Cleaning operations should be performed routinely, with frequency based on area classification, usage, risk, and visible cleanliness.

残留物质，颗粒以及微生物的累计都可能受表面自身的影响。不规则的表面或多孔的表面可容纳残留物质以及其他污染物，使得表面难以清洁和消毒。合适的清洁系统对成功的将设备表面准备好消毒非常重要。清洁操作应定期进行，其清洁频次应按照区域级别，功能，风险以及可见清洁程度而定。

A good cleaning agent is formulated to contain an effective surfactant system that will support the water in its efforts to release particles, residues, and other foreign materials. Procedurally, strict cleaning (without the use of a sanitizer, disinfectant, or sporicide) should be conducted on a routine basis as defined by written procedures.

好的清洁试剂应包含有效表面活性剂,以助于将粒子,残留以及其他外来物料溶解在水里面。严格的清洁程序（不含洗手液，消毒液以及杀孢子剂的使用）应以日常清洁为基础，并以书面形式规定下来。

9.1 Area Classifications and Cleaning and Disinfecting 区域级别，清洁和消毒

Approaches 方法

Area classification for controlled environments based on airborne particulate levels have been in use for many years. The classifications used are based on one retired and two active industry standards (Table 9.1-1):

依据空气中粒子水平来定义受控环境的级别的方法已流行多年，该分级方法的制定依靠于一种已作废以及两种仍适用的企业标准（表9.1-1）

- U.S. Federal Standard 209E : Defining Classes 100,1,000,10,000, and 100,000 (14)*
- 美国联邦标准209E：百级，千级，万级以及十万级（14）定义*
- EU Annex 1: Defining Grades A, B, C, and D (5)
- EU 附录1：级别A，B，C和D级别的定义（5）
- ISO 14644: Defining ISO Classes 5, 6, 7, and 8 (15)
- ISO 14644:ISO 5,6,7和8级别（15）的定义

*Obsolete U.S. Federal Standard 209E classification added for continuity.

已过时的美国联邦标准209E

Terminology and adherence to specific guidelines varies among GMP firms throughout the world. U.S. federal standard 209E was retired in 1999, paving the way for worldwide harmonization by new clean room protocols from the International Organization for Standardization (ISO). The following table provides a comparison of these standards.

全球不同团体发布的GMP规范以及特定指南中的术语都有所不同。而美国联邦标准209E在1999年被废弃，代之采用ISO发布的洁净房间分级方法。下表提供了三种标准之间的比较。

Table 9.1-1 Area Classifications

Cleanroom Standards - Airborne Particulate Limits (particulates/m3) *(13)*

Particle size	ISO 14644	U.S.FDA (Aseptic Processing Guidance)	USP <1116>	EU Annex 1 and WHO Annex 4	Japan (Aseptic Processing Guidance)	JP XVI
	ISO 5	Class 100[1,2]	ISO 5/Class 100	Grade A Grade B (at rest)	Grade A Grade B (at rest)	Grade A Grade B (at rest)
≥0.5μm	3,520	3,5200[3]	3,520	3,500	3,520	3,520
≥5μm	29	Not specified	Not specified	20[4]	20	Not specified
	ISO 6	Class 1000	ISO 5/Class 1000	N/A	N/A	N/A
≥0.5μm	35,200	35,200	35,200	N/A	N/A	N/A
≥5μm	290	Not specified	Not specified	N/A	N/A	N/A
	ISO 7	Class 10,000	ISO 7/Class 10,000	Grade B (in operation)	Grade B (in operation) Grade C (at rest)	Grade B (in operation) Grade C (at rest)
≥0.5μm	352,000	352,000	352,000	350,000	352,000	352,000
≥5μm	2,900	Not specified	Not specified	2,900	2,900	Not specified
	ISO 8	Class 100,00	ISO 8/Class 100,000	Grade C (in operation) Grade D (at rest)[5]	Grade C (in operation) Grade D (at rest)	Grade C (in operation) Grade D (at rest)
≥0.5μm	3,520,000	3,520,000	3,520,000	3,500,000	3,520,000	3,520,000
≥5μm	29,000	Not specified	Not specified	29,000	29,000	Not specified

表9.1-1 区域级别

洁净房间的标准-空气中微粒限度（微粒/ m^3）（13）

尘粒径	ISO 14644	美国FDA（无菌工艺指南）	美国药典<1116>	欧盟附录1和WHO附录4	日本（无菌工艺指南）	日本药典XVI
	ISO 5	Class 100[1,2]	ISO 5/百级	A级 B级（静态）	A级 B级（静态）	A级 B级（静态）
≥0.5μm	3,520	3,5200[3]	3,520	3,500	3,520	3,520
≥5μm	29	未指定	未指定	20[4]	20	未指定
	ISO 6	Class 1000	ISO 5/千级	N/A	N/A	N/A
≥0.5μm	35,200	35,200	35,200	N/A	N/A	N/A
≥5μm	290	未指定	未指定	N/A	N/A	N/A
	ISO 7	Class 10,000	ISO 7/万级	B级（动态）	B级（动态） C级（静态）	B级（动态） C级（静态）
≥0.5μm	352,000	352,000	352,000	350,000	352,000	352,000
≥5μm	2,900	未指定	未指定	2,900	2,900	未指定
	ISO 8	Class 100,00	ISO 8/十万级	C级（动态） D级（静态）[5]	C级（动态） D级（静态）	C级（动态） D级（静态）
≥0.5μm	3,520,000	3,520,000	3,520,000	3,500,000	3,520,000	3,520,000
≥5μm	29,000	未指定	未指定	29,000	29,000	未指定

1. Class 100 and Grade A are defined as requiring unidirectional airflow by all applicable guidelines.

   所有可用指南中百级和A级都是定义为非单向流。

2. Obsolete U.S. Federal Standard 209E classification added for continuity.

   已废除的美国联邦标准209E分级加入以保持连续性

3. Class titles for U.S. FDA and USP indicate equivalent particle counts per cubic foot.

   U.S. FDA 和美国药典中级别名称代表相同粒子数每立方英尺

4. ISO 4.8 based on reduced limit for particles >5 μm.

   ISO4.8 在大于5.0微米粒子数的基础上降低了其限制；

5. Grade D operational particulate counts depend on the operation and are not defined by any guideline

D级动态粒子数目决定于其操作，且未在任何指南中有定义。

In addition to standards on airborne particulates, guidance for microbial action levels for classified areas has also been established (Table 9.1-2).

除尘埃粒子外，各级别的微生物行动限也一起发布了（表9.1-2）

Table 9.1-2 Environmental Monitoring Requirements/Guidance *(13)*

表9.1-2环境监控要求/指导原则（13）

Monitoring Guidance 监测指南	U.S.FDA (Aseptic Processing Guidance) 美国FDA（无菌工艺指南）	USP<1116> 美国药典<1116>	EU Annex 1, PIC/S and WHO Annex 4 欧盟附录1，PIC/S和WHO附录4	Japan (Aseptic Processing Guidance) 日本（无菌工艺指南）	JP XVI 日本药典XVI
Frequency (Airborne total particulate and viable count Surface viable count, Personnel sampling as noted)	Class 100: Each production shift Gloves daily or each lot. Other classes not specified.	ISO 5: Each production shift. ISO 7: Each operating shift ISO 8: Twice per week	A: In operation, continuous particulate monitoring required for critical operations. Frequent viable sampling. B: In operation, frequent particle monitoring is required. C, D: Monitoring on risk basis. Surfaces and personnel should be monitored after critical operations.	A, B: Each operating shift for airborne micro, surfaces and personnel; continuous particulate monitoring. C, D: Airborne micro twice per week; airborne particulate once per month; personnel not required.	A: Each operating shift. B: Each operating shift. C, D (potential product/container contact): Twice per week C, D (No potential product/container contact): Once per week
频次（尘埃粒子总颗粒和活性计数、表面活性计数、人员取样）	百级：每个生产班次 手套每天或每批 其它级别未指定	ISO 5: 每个生产班次 ISO 7: 每个运行班次 ISO 8: 每周两次	A．动态，关键操作要求持续颗粒监测。频繁的可行取样。 B．动态，要求频繁地颗粒监测 C.D.根据风险进行监测。表面和人员应在关键操作后进行监测。	A.B：每个运行班次监测尘埃微粒，表面和人员，持续监测颗粒 C.D: 尘埃微粒每周2次，尘埃粒子每月一次	A．每个运行班次 B．每个运行班次 C.D（可能的产品/容器接触）每周2次 C.D.（无潜在的产品/容器接触）：每周一次
Airborne viablel action levels (Active air sampling)	Calss 100: 1 CFU/m^2 Class 10,000: 10 CFU/m^2 Class 100,000: 100 CFU/m^2	Recommends use of incident rate (% of samples with micro contamination) rather than count levels, as follows [2]: ISO 5: <1%　ISO 7: <5% ISO 6: <3%　ISO 8: <10% Applies to all active air, passive air and surface samples	A: <1CFU/m3　C:100 CFU/m3 B: 10 CFU/m3　D: 200 CFU/m3	A: <1CFU/m3　C:100 CFU/m3 B: 10 CFU/m3　D: 200 CFU/m3	A: <1CFU/m3　C:100 CFU/m3 B: 10 CFU/m3　D: 200 CFU/m3 0.5m3 sample required for A, B 0.2 m3 sample required for C, D
尘埃粒子可行行动水平（主动空气取样）	百级：1CFU/平方米 万级：10CFU/平方米 十万级：100CFU/平方米	推荐使用事故率（微粒污染取样百分比）而不要使用计数水平，如下： ISO 5: <1%　ISO 7: <5% ISO 6: <3%　ISO 8: <10% 适用于所有主动取样、被动取样和表面取样。	A: <1CFU/m3　C:100 CFU/m3 B: 10 CFU/m3　D: 200 CFU/m3	A: <1CFU/m3　C:100 CFU/m3 B: 10 CFU/m3　D: 200 CFU/m3	A: <1CFU/m3　C:100 CFU/m3 B: 10 CFU/m3　D: 200 CFU/m3 A.B取样量0.5m3 C.D取样量0.2 m3
Airborne viable action levels (Passive air sampling)	Calss 100: 1 CFU/m^2 Class 10,000: 10 CFU/m^2 Class 100,000: 50 CFU/m^2	Same sample incident rate as active air. 90 mm diameter settle plate/4	A: <1CFU/m3　C:50 CFU/m3 B: 5 CFU/m3　D: 100 CFU/m3	A: <1CFU/m3　C:50 CFU/m3 B: 5 CFU/m3　D: 100 CFU/m3	Not specified

	90 mm diameter settle plate/4 hr Use of sttling plates is optional	hr	90mm diameter settle plate/4hr	90 mm diameter settle plate/4hr.	
尘埃粒子行动水平（被动空气取样）	百级：1CFU/平方米 万级：10CFU/平方米 十万级：50CFU/平方米 90mm直径沉降碟/4小时 是否使用沉降碟是可选的	与主动空气取样采用相同的样品事故率 90mm直径沉降碟/4小时	A: <1CFU/m3 C:50 CFU/m3 B: 5 CFU/m3 D: 100 CFU/m3 90mm 直径沉降碟/4小时	A: <1CFU/m3 C:50 CFU/m3 B: 5 CFU/m3 D: 100 CFU/m3 90 mm 沉降碟/4小时	未指定
Surface viables action levels [(1)]	Not specified	Same sample incident rate as active air. Use contact plat or swab.	A: <1 C:25 B: 5 D: 100 55 mm diameter contact plate	A: <1 C:25 B: 5 D: 50 24-30 cm2 contact or swab area	A: <1 C:25 B: 5 D: 50 24-30 cm2 (5.4-6.2 cm diameter contact or 25 cm2 swab area)
表面行动水平	未指定	与主动空气取样采用相同的样品事故率 使用接触碟或擦拭取样	A: <1 C:25 B: 5 D: 100 55 mm 接触碟	A: <1 C:25 B: 5 D: 50 24-30 cm2 接触或擦拭区域	A: <1 C:25 B: 5 D: 50 24-30 cm2 (5.4-6.2 cm 直径接触碟或25cm2 擦拭区域)
Personnel viables action levels (gown)	Not specified. Gown sampling must be established based on job responsibility.	Same sample incident rate as active air, [(4)]	Not specified	Not specified	Not specified
人员行动水平（更衣）	未指定 必须根据岗位职责来建立更衣取样	与主动空气取样采用相同的样品事故率	未指定	未指定	未指定
Personnel viables action levels (gloves)	Not specified	Same sample incident rate as active air.	Glove print, 5 fingers A: <1 CFU/glove B: <5 CFU/glove	Glove print, 5 fingers A: <1 CFU/5 fingers B: <5 CFU/5 fingers	Glove print, 5 fingers A: <1 CFU/5 fingers B: <5 CFU/5 fingers
人员行动水平（手套）	未指定	与主动空气取样采用相同的样品事故率	手套印，5指 A: <1 CFU/手套 B: <5 CFU/手套	手套印，5指 A: <1 CFU/5指 B: <5 CFU/5指	手套印，5指 A: <1 CFU/5指 B: <5 CFU/5指

1. Guidance is condensed. Refer to the cited references for complete guidance
   此处为精简信息，欲知详情请参照完整指导原则。
2. FDA guidance retains count limits rather than overall contamination rate
   FDA 指南保留计数限制方法，而不是总污染率
3. In general, surface and personnel monitoring should not interfere with the class protection and should be done after critical operations
   一般来说,表面监控和人员监控不应对洁净环境保护造成干扰，应在关键操作结束后进行。
4. Operators may not be aseptically gowned in ISO 8 support areas
   操作员也许未在ISO8洁净级别下进行更衣。

9.1.1 Cleaning and Disinfecting Grade A (ISO 5) and Grade B A级（ISO5）和B级的清洁和消毒

(ISO 5 at Rest, 6/7 in operation) Areas（静态ISO5，动态ISO6/7）区域

Cleaning and disinfecting these areas take on three varying procedures:

对这些区域进行清洁消毒包含不同的三个程序：

- Cleaning and disinfecting conducted on an established frequency.
- 按照已确定的频次进行清洁和消毒。
- Cleaning and disinfecting conducted in response to an adverse trends and/or a return from a shutdown.
- 在出现不良趋势和空调关闭重新开启后进行清洁和消毒
- Routine disinfection conducted without a prior cleaning step
- 没有进行清洁的日常消毒

These areas traditionally incorporate 100% HEPA-filter modules in the ceilings, and, thus, the filter should not be exposed to cleaners or antimicrobial chemical agents on a routine basis. Accidental wetting of the filter matrix with a cleaner or disinfecting agent can cause the proliferation of microorganisms and degradation of the filter matrix, which can lead to the integrity of the filter system being compromised.

通常来说，这些区域的天花板上安装的效率为100%的高效过滤器，因此这些过滤器不应该经常暴露于清洁剂和抗微生物化学试剂。滤芯偶尔被清洁剂或消毒剂弄湿容易导致微生物的滋长以及滤芯介质的降解，从而导致过滤系统的完整性受损。

For cleaning and disinfecting conducted on an established frequency in the Grade A and Grade B areas the following order is commonly followed (from lowest bioburden to highest bioburden) to ensure contamination from the cleaning process itself is minimized.

为保证清洁步骤本身对A级和B级区域的污染降到最低，通常按照以下步骤对其按照确定的频次进行清洁和消毒：

- A sterile cleaning agent (high surfactant based product) is applied to ceilings (not HEPA filters), then walls, then equipment is cleaned and finally the cleaning agent is applied to the floors in a succession from the furthest point to the closest point to the room exit. Mopping is the preferred method of application for ceilings, walls and floors.
- 无菌清洁试剂（高表面活性剂）先用于清洁天花板（非HEPA过滤器），然后墙壁，再是设备表面，最后按照离房间出口由远及近的顺序对地面进行清洁。而用拖把擦是清洁天花板，墙壁和地面的首选方法。
- A squeegee is used to remove the excess liquid and contaminants from the ceiling (not HEPA filters), then walls and floors again in a succession from the furthest point to the closest point to the room exit.
- 用橡胶滚轴清洁器去除天花板（非HEPA过滤器），然后墙壁，并最后同样按照离房间出口由远及近的顺序将地面去除多余的液体和污染物。
- The dirtied liquid should be lifted from the area via a sterile dry mop, sterile dry wipe, or HEPA filtered wet vacuum. This prepares the surface for the disinfecting agent.
- 弄脏的液体应用无菌干拖把，无菌干擦或HEPA湿真空过滤装置从区域去除，该步骤是为表面消毒做好准备。

- After the surfaces have dried they should be sufficiently wetted with a sterile disinfecting agent via mop, spray or wipe following the same sequence being used for the ceiling (not HEPA filters), walls, and floors as described above.
- 当表面干燥以后，应通过拖，喷或擦，并同样按照天花板（非HEPA过滤器），然后墙壁以及地面（按照上述同样顺序）将表面用无菌消毒试剂完全湿透，

In cases where the cleaning and disinfection is being performed in response to an adverse event or a return form a shutdown the cleaning and disinfection process may need to be repeated for several cycles to ensure the area bioburden is reduced to acceptable levels.

当清洁和消毒是针对有不良事件产生或是空调关闭后重新开启的情况，应多次重复清洁和消毒的步骤以保证该区域的生物负载降低到可接受水平。

The frequency of the cleaning and disinfection steps may be different with disinfection occurring more frequently. In these cases where disinfection is performed without a prior cleaning the application of the disinfecting agent should follow the same sequence being used for the ceiling, walls, and floors as described above.

清洁和消毒的频次有可能会不一样，消毒的频次更高一些。在这些未经过事先清洁的情况下，消毒试剂仍应按照以上描述的相同顺序进行消毒。

Grade A and B work surfaces, and equipment (production lines, dedicated carts, tanks, racks, etc) should be wiped using a sterile cleaning agent and a dry wipe. The dry wipe is used to soak up contaminants in the liquid. After assured drying the surface should be sufficiendy wetted with a sterile disinfectant or sporicide. Items found in the cleanroom represent an equivalent contamination level to other surfaces in the clean room (ceilings, walls and floors) as they are also exposed to sources of contamination present within the area.

A和B级区域的工作表面，以及设备（生产线，专用小车，罐体，以及支架等）应用无菌清洁试剂和干燥抹布擦拭。干燥抹布用来吸取液体中的污染物。当确定干燥后，其表面应用无菌消毒剂以及杀孢子剂湿透。在洁净区中的其他物品的污染水平与其他表面（天花板，墙壁以及地面）等同，因为它们同样暴露于该区域中存在的污染源。

In general the cleaning frequency for Grade A and Grade B areas as well as work surfaces and equipment should be based on the facility design, area classification, usage (process being performed), risk, and visible cleanliness. See Section 10.0.

A和B级区域以及工作表面和设备的清洁频次的制定应基于设施的设计，区域的洁净级别，功能（所用工序），风险以及可见异物。详见第10部份。

9.1.2 Cleaning and Disinfecting Grade C (ISO 7 at rest / ISO 8 in operation) and Grade D (ISO 8 at rest) Areas
Cleaning and disinfecting of these areas also take on three varying procedures that are similar to those required in Grade A (ISO 5) and Grade B (ISO 5 at rest/6 /7in operation):

C级和D级区域的清洁消毒（ISO7 静态和ISO8 动态）以及D级（ISO 8 静态）也有与A 级(ISO 5) and B级(ISO 5 静态/6 /7动态)类似的3个不同程序

- Cleaning and disinfecting conducted on an established frequency.
- 按照已确定的频次进行清洁和消毒
- Cleaning and Disinfecting conducted in response to adverse trends and/or a return from a shutdown.
- 在出现不良趋势和空调关闭重新开启后进行清洁和消毒
- Routine disinfection conducted without a prior cleaning step
- 没有进行清洁的日常消毒

These areas traditionally incorporate partial HEPA-filter modules in the ceilings, and, thus, the filter should not be exposed to cleaning or disinfecting agents on a routine basis. Accidental wetting of the filter matrix with a cleaner or antimicrobial chemical agent can cause the proliferation of microorganisms and degradation of the filter matrix, which can lead to the integrity of the filter system being compromised.

通常来说，这些区域的天花板上安装的高效过滤器占了部分面积，因此这些过滤器不应该经常暴露于清洁剂和抗微生物化学试剂。滤芯偶尔被清洁剂或消毒剂弄湿容易导致微生物的滋长以及滤芯介质的降解，从而导致过滤系统的完整性受损。

For cleaning and disinfecting conducted on an established frequency the walls, ceilings, and floors of Grade C and Grade D areas should be cleaned in the following manner. First, a sterile or nonsterile cleaner (high surfactant based product) is applied to ceilings (not HEPA filters), then walls, then equipment is cleaned and finally the cleaner is applied to the floors in a succession from the furthest point to the closest point to the room exit. Mopping is the preferred method of application for ceilings (not HEPA filters), walls and floors.

对C级和D级区域的墙面，天花板，地板应按以下顺序按照固定频率进行清洁。首先，无菌清洁试剂（高表面活性剂）先用于清洁天花板（非HEPA过滤器），然后墙壁，再是设备表面，最后按照离房间出口由远及近的顺序对地面进行清洁。而用拖把擦是清洁天花板，墙壁和地面的首选方法。

Then a squeegee should be used to remove used to remove the excess liquid and contaminants, and finally a HEPA-filtered wet vacuum or other means of lifting the liquid from the area should be employed. After assured drying the surface should be sufficiendy wetted with a sterile or nonsterile disinfecting agent via mop, spray or wipe.

用橡胶滚轴清洁器去除天花板（非HEPA过滤器），然后墙壁，并最后同样按照离房间出口由远及近的顺序将地面去除多余的液体和污染物。当表面干燥以后，应通过拖，喷或擦，并同样按照天花板（非HEPA过滤器），然后墙壁以及地面（按照上述同样顺序）将表面用无菌消毒试剂完全湿透，

In cases where the cleaning and disinfection is being performed in response to an adverse event or a return form a shutdown the cleaning and disinfection process may need to be repeated for several cycles to ensure the area bioburden is reduced to acceptable levels.

当清洁和消毒是针对有不良事件产生或是空调关闭后重新开启的情况，应多次重复清洁和消毒的步骤以保证该区域的生物负载降低到可接受水平。

The frequency of the cleaning and disinfection steps may be different with disinfection occurring more frequently. In these cases where disinfection is performed without a prior cleaning the application of the disinfecting agent should follow the same sequence being used for the ceiling, walls, and floors as described above.

清洁和消毒的频次有可能会不一样，消毒的频次更高一些。在这些未经过事先清洁的情况下，消毒试剂仍应按照以上描述的相同顺序对天花板，墙面，地板进行消毒。

Grade C and D work surfaces and equipment (production lines, racks, tanks, dedicated carts, etc.) should be cleaned using a sterile or non-sterile cleaning agent and a dry wipe. The dry wipe is used to soak up contaminants in the liquid. After assured drying the surface should be sufficiently wetted with a sterile or non-sterile disinfecting agent. Items found in the cleanroom represent a possibly equivalent contamination level as ceilings, walls and floors as they are exposed to possibly existent contamination within the area.

C和D级的工作台面和设备（产品线，架子，罐，和专用推车等）应该用无菌或非无菌的清洁剂和干布清洁。干布用来吸出液体中的污染物。当表面干燥后，再用无菌和或非无菌的消毒剂充分湿润。洁净区中的物体与天花板，墙壁和地板暴露在相同环境区域中，因此代表该区域的污染水平。

In general the cleaning frequency for Grade C and Grade D areas as well as work surfaces and equipment and the

use of a sterile or non-sterile cleaning and disinfecting agent should be based on the facility design, area classification, usage (process being performed), risk, and visible cleanliness. See Section 10.0.

通常来说，C和D级区域包括工作台面，设备的清洁频次以及无菌和非无菌清洁和消毒试剂的使用依赖于设施的设计，区域的级别，功能（工序），风险以及可见清洁程度。详见10.0.

9.2 Application Methods 应用方法

Four basic methods of application for a cleaning or disinfecting agent are in use today. The method selected is based in part on the design of the facility. Safety precautions should be taken when using these agents. See Appendix V for more information.

目前有四种清洁和消毒试剂使用方式。使用方法的选择取决于设施的设计。在使用这些试剂时应采用安全措施。详见附录V。

- **Spraying 喷洒**

This method produces the best wetting of surfaces. A spraying method that employs larger rather than smaller droplets has been found to provide better wetting results. As efficacy performance is based on saturation and penetration of the cell wall as well as contact time, this method produces very good results as long as the underlying surface has been appropriately cleaned. Spraying does not clean the surface, as it lacks mechanical action. Consistent spraying without routine use of a mechanical cleaning action will potentially result in the development of high residue levels, entrapped particulates, deteriorated surfaces, and, as the decontaminating agent will be unable to reach viable contaminants, increased bioburden levels.

该方法能使得表面充分湿润。已有证据表明，用大液滴喷洒比小液滴喷洒更能使得表面湿润。细胞壁的饱和度和穿透性以及作用时间决定消毒剂效力，因此只要物体表面已经过合适的清洁，该方法效果良好。喷洒不能清洁表面，因为它缺乏机械动作。持续的喷洒而没有机械的清洁动作将导致高残留水平，颗粒表面被包埋，物体表面恶化，并且，由于净化剂无法接触生物污染物，从而导致生物负载水平升高。

- **Mopping 拖地**

Mopping assures that a mechanical action of cleaning is employed. The use of a mopping system for either walls or floors removes residues, viable contamination, and nonviable contamination.

拖地保证了清洁中采取了机械运动。用拖把来拖墙壁或地板能去除残留，生物污染以及非生物污染。

For walls, mopping is done from the highest surface point to the lowest surface point. For floors, mopping is done from cleanest to dirtiest and from the highest grade to the lowest grade. While mopping provides the mechanical action needed, great care must be taken to ensure surfaces are wetted appropriately. In general, mopping does not provide as uniform wetting as spraying. For example, the wringing of mop heads and the inability for mop heads to hold sufficient liquid may compromise the level of surface wetting and, therefore, the contact time required. As a result, while cleaning is accomplished, disinfection may be compromised.

拖墙壁时，拖把应从最高点到最低点。拖地板时，拖把应从最干净点到最脏点，以及从高级别区到低级别区域。在拖把进行机械清洁的同时，也应保证待清洁表面充分湿润。通畅来说，拖不能像喷洒一样使表面均匀湿润。比如，将拖把头拧干以及拖把头无法保持足够的液体使得表面湿润水平不足，因此，作用时间非常重要。因此清洁完成后，消毒效果也许会打折扣。

- **Wiping 擦拭**

Wiping with a presaturated cloth or a dry wipe that is wetted with a cleaning or disinfecting agent is a common practice in the cleaning industry. Wiping, as with mopping, cleans the surface of residues, viable contamination, and nonviable contamination with a mechanical action. Normally, wiping is associated more with cleaning than disinfection. Wiping is done on smaller surfaces that need to be cleaned, such as door handles, push plates, return

vents, equipment, carts, and pass-through areas. **While wiping possesses the ability to clean the surface, as with mopping, disinfection can be compromised as the surface wetting may not be sufficient to provide the required amount of disinfecting agent contact time. While wiping may remove viable contamination, great care must be taken to ensure that surfaces are adequately wetted.**

用饱和的布或干布用清洁剂或消毒剂浸湿擦拭在清洗行业的普遍做法。擦拭，同拖一样，用机械的方式清洁表面的残留，活体污染，以及非活体污染。擦拭通常与清洁有关，而不是消毒。擦拭用于较小的需要清洁的物体表面，如门把手，推板，返回通风孔，设备，推车，并通过区域。当擦拭用于清洁物体表面，同拖一样，可能因为表面留有足够的消毒剂的量和消毒时间以至于无法充分湿润使得消毒效果减弱。当用擦拭来去除活体污染物，必须保证表面被充分湿润。

- **Fogging or Gassing 雾或气体**

This method can produce excellent results but does require longer periods of time to ensure adequate distribution of the agent and sufficient surface contact time. Fogging methods generate very fine droplets of the disinfecting agent, whereas gassing use a disinfecting agent in a gas form. While both are very effective, just as with spraying, they do not clean the surface**.** As a result, fogging or gassing without routine use of a mechanical cleaning action will potentially result in the development of high residue levels, entrapped particulates, deteriorated surfaces, and, as the decontaminating agent will be unable to reach viable contaminants, increased bioburden levels. Chemical agents that have commonly been used with this method of application are peracetic acid, hydrogen peroxide, phenol, bleach, quaternary ammonia, paraformaldehyde, and chlorine dioxide**.** Great care must be taken when a decision is made to use this method, as special safety considerations are required due to the potential exposure dangers and explosion hazards. See Appendix VIII for additional information on this method.

这种方法可以产生良好的效果，但需要较长的时间，以确保试剂能充分分布，并且有足够的表面接触时间。雾化的方法能使消毒剂生成均匀颗粒，而气体方法使消毒剂成为气体。两种方法都很有效，但同喷洒一样不能清洁表面。因此，只有雾和气体方法而没有机械的清洁动作将导致高残留水平，颗粒表面被包埋，物体表面恶化，并且，由于净化剂无法接触生物污染物，从而导致生物负载水平升高。用于该方法的常用化学试剂有过氧乙酸，过氧化氢，苯酚，漂白剂，季氨，甲醛，二氧化氯。使用该方法时应该非常小心人体这些化学试剂的暴露风险以及这些化学试剂潜在的易爆风险。该方法的更多详情请参见附录**VIII。**

As part of a cleaning and disinfection program, a combination of multiple application methods is suggested for attaining successful results.

为获得最好的效果，清洁和消毒程序应最上述方法综合使用。

9.3 Cleaning and Disinfecting Materials and Workstations 清洁和消毒材质和工作台面

9.3.1 Cleaning and Disinfecting Curtains 清洁和消毒帘布

A multitude of curtain material substrates can be used in clean room operations. The most common is vinyl. Cleaning curtains is a difficult but critical activity. Curtain materials are generally considered more difficult to clean and disinfect due to their softer surface finish which when viewed microscopically is rougher containing areas where dirt and microorganisms can be better protected from the cleaning and disinfecting agents. To ensure the disinfecting agent is effective curtains should be first cleaned to remove any dirt that may be present and then disinfected.

洁净室操作中会用到各种帘布材质。最常用的是乙烯基。清洁帘布非常困难也非常重要。帘布材质质地柔软，在显微镜下观察时可以发现，它表面粗糙，可以保护污垢以及微生物与清洁和消毒剂接触，通常被认为很难清洁和消毒。为确保消毒剂效果有效，帘布应首先进行清洗，以去除可能存在的污垢，随后进行消毒。

Cleaning should utilize a high-surfactant-based cleaning product or 70% isopropyl alcohol that is applied via a

mechanical cleaning action (wiping or mopping). After cleaning, the curtains should be disinfected with a disinfectant or a sporicide that is characteristically low in residue (for example, H202 or Peracetic Acid). Curtain surfaces should be sprayed or wiped with an efficacious disinfectant or sporicide and allowed to remain wetted for the contact time validated in antimicrobial effectiveness studies. This time is normally a minimum of five minutes. Curtains should be cleaned with a greater frequency than wall surfaces, as they may come in contact with personnel more frequently.

清洗时应采用较高的表面活性剂的清洁产品或70%异丙醇，并采用机械清洗方法（擦或拖）。清洁后，帘布用消毒剂或残留较少的除孢子剂进行除菌（如H202 或过氧乙酸）。帘布表面用有效消毒剂或杀孢子剂喷洒或擦拭，并使其保持湿润一段时间，该时间需经过抗菌有效时间研究验证。该时间通常最少5分钟。帘布应比墙表面更常清洁，因为他们经常会与人体接触。

If a disinfectant or sporicide with medium to high residue is utilized, such as phenolic, quaternary ammonium, or bleach, the curtains should be subsequently wiped using 70% IPA and a dry wipe to assure a majority of residue has been removed. The transfer of residue from curtains to critical areas should be avoided. The spraying of a disinfectant or sporicide should be targeted to curtains to avoid overspray to other surfaces, including filling equipment.

如果使用残留物中到高的消毒剂或杀孢子剂，比如如酚类，季铵，或漂白剂，帘布应该再用70% IPA或干部擦拭，保证残留最大限度被去除。应避免残留从帘布被穿衣到关键区域。喷洒消毒剂或除孢子剂应准确喷洒到帘布上，以避免喷洒到其他表面，包括灌装机。

9.3.2 Cleaning and Disinfecting Unidirectional Airflow Hoods, Benches, and Biosafety Cabinets 清洁和消毒层流罩，长凳，以及生物安全柜

Unidirectional airflow hoods, benches, and biosafety cabinets are used by most GMP operations for a multitude of tasks. Most commonly, the workstations are used for the manipulation or transfer of cells or cell cultures, manipulations of drug products, compounding, or aseptic transfers. The cleaning and disinfecting of unidirectional air flow hoods, benches, and biosafety cabinets is commonly done before and after use.

层流罩，长凳以及生物安全柜被应用与很多GMP生产中。最常见的是用于手工转移细胞和培养液的工作台，药物产品的操作，合成，以及无菌转移。层流罩，长凳以及生物安全柜通常在其使用前和使用都需要清洁和消毒。

Cleaning of the interior surfaces requires first cleaning the surface of any residual or spillage. Residing residual or spillage will adversely affect disinfection by blocking the chemical agent from contacting the microorganisms on the surface. The surface should be first cleaned using a cleaner with sufficient surfactants or, at a minimum, sterile 70% IPA. The agents should be sprayed onto the surface and wiped with a dry wipe throughout the enclosure. Wiping should occur from the top of the unit to the bottom of the unit and from the rear of the unit to the front of the unit and should include all sides and the work surfaces. During cleaning, the filter and filter grate (either vertical or horizontal) should not be wetted. Wetting of the filter with the cleaning or disinfecting agent will provide a suitable habitat for the growth of molds and can cause damage to the filter itself.

内表面的清洁首先要求去除残留和溢出物残留或溢出物会通过阻碍化学试剂接触表面微生物而影响消毒。表面通过足够的表面活性剂或清洁剂，最少无菌70% IPA进行清洁。将试剂喷洒到表面，并用抹布擦拭表面。擦拭应从顶部擦到地步，从后面擦到前面，并包含所有面以及工作表面，清洁期间，过滤器和滤栅（垂直或水平的）不应被弄湿。用清洁或消毒剂湿润过滤器将为霉菌的生长提供合适的栖息地，并会对过滤器本身造成损害。

Once the cleaning step is complete, the surface should be disinfected with an appropriate disinfecting agent. The use of a disinfecting agent such as phenols or quaternary ammoniums will be less effective than using sporicidal

agents and will leave residues that are more difficult to remove. For that reason, they are not the preferred chemical agents for the reduction of microorganisms in a workstation environment.

一旦清洁步骤完成，应用合适的消毒剂对表面进行消毒。消毒剂如酚或季铵盐的使用比使用杀孢子剂效力低，并且会留下更难清除的残留物。因此，酚和季铵类并非用于减少工作台环境微生物的首选化学试剂。

Sporicidal agents are normally applied with a wetted wipe. Sporicides may be sprayed, but vapors may be increased and care should be taken to assure safe levels are maintained. After use of the sporicidal agent, an IPA wipe (dry wipe and 70% IPA) is required if the sporicidal agent leaves a residue.

除孢子剂通常用湿布擦。除孢子剂可用于喷洒，但会增加蒸发，因此应保证维持灭菌有效水平。除孢子剂使用后，如果该试剂会有残留，应再使用IPA擦拭（干擦或使用70%IPA）。

Sporicidal agents such as 0.52% sodium hypochlorite or peracetic acid will leave a residue and require a wipe-down after use, while 6% hydrogen peroxide will not leave a residue and will not require a subsequent wipe-down.

杀孢子剂如0.52%的次氯酸钠和过氧乙酸容易有残留，使用后需要再擦拭，而6%过氧化氢不会留下残留物，使用后不需要再进行擦拭。

9.4 Cleaning and Disinfecting Equipment Surfaces 清洁和消毒设备表面

9.4.1 Non-product-contact Equipment Surfaces 非产品接触设备表面

Non-product-contact equipment surfaces can be found in areas that are close to product-contact surfaces.

非产品接触设备的表面可能存在接近产品接触表面的区域。

Due to their critical location, caution should be taken to assure that cleaning chemicals, sanitizers, disinfectants, sporicides, wipers, and other items used on the surface do not leave a residue that may be transferred inadvertendy to a product-contact surface. Residues from chemical agents, fibers from wipers, and released wiper binders and wiper size can be sources of possible contamination.

由于其所在位置关键，因此应确保化学清洁剂，杀菌剂，消毒剂，除孢子剂，擦拭布，以及用在表面的其他物品不会有残留，并不可逆的转移到产品接触表面。从化学试剂，擦拭布的纤维，擦拭布的绑带，以及擦拭布的涂料所留下可能会成为潜在污染物。

Equipment should be precleaned for any past product spills, broken glass (from vials, syringes, ampules, etc.), torn stoppers, damaged caps, and other foreign matter before attempting disinfection.

进行消毒灭菌前，设备应将前批溢出产品，破碎的玻璃（如玻璃品，注射器，安瓿西林瓶），破损的塞子，损坏的盖子，和其他异物清洁干净。

Once precleaning of the equipment is performed, the surface should be sprayed or wiped with an efficacious disinfectant or sporicide and allowed to remain wetted for the specified contact time. After the specified time, all surfaces should receive a wipe-down using 70% IPA if a sporicide or disinfectant with residual properties is used.

一旦设备预清洁完成，将设备表面用有效的除菌剂和除孢子剂进行喷洒或擦拭，并使其在规定的作用时间保持湿润。规定时间过后，如果所用除菌剂和除孢子剂会有残留，所有表面都应用70% IPA再进行擦拭。

9.4.2 WorkSurfaces 工作台面

Work surfaces, such as work tables, carts, and setup areas, may also be near product or near components that come in contact with product. Precleaning of these surfaces should be done routinely in addition to disinfection. Routine cleaning before disinfection provides a higher level of disinfection efficacy. After cleaning, surfaces should be disinfected using either a disinfectant or a sporicide. The determination for the type of product to be used will depend on the defined risk to product or product components. After the use of a disinfectant or sporicide,

a 70% IPA spray-down followed by a dry wipe may be required if the disinfectant or sporicide used is determined to leave a residue. Frequency of cleaning is normally daily but should be based on usage.

工作台表面，如工作桌、推车和安装区域，都有可能在产品或与产品直接接触的部件附近。这些表面也应该进行日常的清洁和消毒。消毒前日常的清洁可使消毒效力较高。清洁后，表面用消毒剂或除孢子剂进行消毒。所使用产品的类型应取决于它对产品或产品配件的风险。如容易残留的消毒剂或除孢子剂使用后，应喷洒70%IPA，并用干布擦拭干净。通常清洁应每天进行，但应参照使用频率。

9.4.3 Nonstructural Clean Room and Hard-to-Clean Surfaces 不规则的洁净室和难清洁表面

Structural surfaces such as walls, ceilings, and floors, along with any filling equipment, should be routinely cleaned and disinfected. The frequency should be based on environmental monitoring results and/or a risk-based analysis. Equal consideration should be given to the routine cleaning and disinfection of nonstructural surfaces that exist in each classification, as these surfaces may contaminate the environmental conditions in the area. Routine scheduling for the cleaning and disinfection of surfaces and any items that may reside on them is a critical function. Surfaces can be divided into two categories: routine nonstructural surfaces and hard-to-clean surfaces. Examples of such surfaces may include those shown in Table 9.4.3-1.

规则表面如墙壁，天花板，以及地板，灌装机应该日常清洁和消毒。频次的确定依据环境监测结果和/或风险分析。但同时，也应考虑各洁净级别中非结构性表面日常的清洁和消毒，因为这些表面会污染洁净环境。对表面和物体上残留的清洁和消毒的日常计划是非常重要的一个职能。表面可以分成两类：常规的非结构表面和难以清洁的表面。该类表面如下表9.4.3-1：

Table 9.4.3-1 Examples of surfaces

Routine nonstructural surfaces 常规非结构性表面	Hard-to-Clean surfaces 难清洁表面
Tanks 柜	Tops of doors 门顶部
Carts 小车	Tracks 小路
Countertops 台面	Conveyers 传送带
Racks 架子	Phones 电话机
Packaged supplies on racks 架子上的包装物	Equipment feet and legs 设备脚和腿
Storage bins 储存罐	Underside of tanks, carts, and equipment 柜子，小车，设备的下面
Stairs 楼梯	Wheels 轮子
Exterior of tubing or pipes 管道外表面	Incubators, refrigerators, and cold rooms 孵化器，冰箱和冷室
Work surfaces 工作台	
Non-product-contact surfaces 非产品接触表面	
Non-product-equipment 非产品设备	

Monitors, samplers, gauges 监控器，取样器，计量器	
Tools (sterilization may be required) 工具（可能需要灭菌）	

Cleaning should be done on all equipment to assure the surface is visibly free from particulate and residue. Disinfection of the surfaces should assure the removal of microbial content to below acceptable surface-monitoring levels. All equipment should be wiped after disinfection by spraying 70% IPA, 70% EtOH, or a high surfactant-based cleaner with little residue that is subsequently wiped with a dry clean room wiper. Cleaning and disinfection frequency of such equipment will depend on the room classification as well as how well contamination is being controlled in the environment and on the equipment.

所有设备都应清洁，以保证没有可见颗粒和残留。表面消毒以保证微生物水平降低到表面可接受监测水平。所有设备应该用70%IPA，70%EtOH或者低残留（可被擦拭去除）的高表面活性剂进行喷洒消毒。这些设备的清洁和消毒频率取决于房间洁净级别，以及环境和设备的污染物的控制水平。

9.5 Cleaning and Disinfecting Tools 工具的清洁和消毒

Tools used in the various room classifications require varying cleaning and disinfection disciplines. A tool is any implement, usually handheld, used for performing and facilitating mechanical operations or adjustments in a classified environment. Examples include forceps, screwdrivers, wrenches, and pliers.

在各种不同级别房间使用的工具应制定不同的清洁和消毒的方式。工具通常用于在不同级别环境下执行或协助机械操作或调整。如钳，螺丝刀，扳手，钳子。

The cleaning, disinfection, or sterilization of a tool is based on the classification of the area in which the tool will be used. A main concern is whether or not the tool is capable of being cleaned, disinfected, or sterilized. Certain tools may incorporate electronics, construction materials, or gasket material that may be adversely affected by such decontamination processes. Another concern is whether the tool will reside in a specific area classification or will be continuously transferred from one area classification to another. The following is not a transfer procedure but rather a suggested practice for the level of cleanliness and disinfection or sterilization state for tools used in varying classifications.

一种工具的清洗、消毒或灭菌取决于该工具将使用的区域洁净级别。主要关注的是是否该工具能够被清洗，消毒，或消毒。某些工具包括电子，建筑材料，或衬垫材料，可能会受到这种清洁过程的不利影响。另一个关注的问题是，该工具是否会驻留在一个特定级别或被不断地从一个区域转移到另一个。以下过程不是一个传输程序，而是对不同级别下工具的清洁和消毒水平或灭菌情况的建议措施：

- For a tool used in Grade D (ISO 8): Tools should be routinely cleaned via a wiping operation that uses a cleaning agent, 70% IPA or 70% EtOH, and a dry wipe or a saturated wiper. This should be done on a routine basis or more frequently based on use of the tool.
- D级（ISO8）：工具应该用清洁剂日常擦拭清洁，70% IPA 或 70% EtOH,干抹布，或饱和擦布。该工作应规定频次进行，或按照工具的使用频率确定。
- For a tool used in Grade C (ISO 7): Tools should be routinely cleaned via a wiping operation that uses a cleaning agent, 70% IPA or 70% EtOH, and a dry wipe or a saturated wiper. A subsequent disinfection step may be performed as needed. This should be done on a routine basis or more frequently based on use of the tool.
- C级（ISO7）：工具应该用清洁剂日常擦拭清洁，70% IPA 或 70% EtOH,干抹布，或饱和擦布。随后的消毒步骤可以按需要进行。该工作应规定频次进行，或按照工具的使用频率确定。

- For a tool used in Grade B (ISO 5/6): Tools should be routinely cleaned via a wiping operation that uses a cleaning agent, 70% IPA or 70% EtOH, and a dry wipe or a saturated wiper. A subsequent sterilization should be performed if feasible. If sterilization is not possible, then a disinfection step (via a sporicidal agent, if possible) should be employed prior to introduction to a Grade B (ISO 5/6) area. This should be done on a routine basis or more frequently based on use of the tool.
- B级（ISO 5/6）：工具应该用清洁剂日常擦拭清洁，70% IPA 或 70% EtOH,干抹布，或饱和擦布。如过工具可以灭菌应随后进行灭菌。如果工具无法进行灭菌，应在该工具放入B级（ISO 5/6）前采取消毒步骤（尽可能用除孢子剂）。灭菌该工作应规定频次进行，或按照工具的使用频率确定。
- For a tool used in Grade A (ISO 5): Tools should be routinely cleaned via a wiping operation that uses a cleaning agent, 70% IPA or 70% EtOH, and a dry wipe or a saturated wiper. A subsequent sterilization of the tool should be performed if feasible. If sterilization is not possible, a disinfection step (via a sporicidal agent, if possible) should be employed prior to introduction to a Grade A (ISO 5) area. This should be done on a routine basis or more frequently based upon use of the tool.
- A级（ISO 5）：工具应该用清洁剂日常擦拭清洁，70% IPA 或 70% EtOH,干抹布，或饱和擦布。如过工具可以灭菌应随后进行灭菌。如果工具无法进行灭菌，应在该工具放入A级（ISO 5）前采取消毒步骤（尽可能用除孢子剂）。灭菌该工作应规定频次进行，或按照工具的使用频率确定。

9.6 Cleaning and Disinfecting Water Points of Use 水点的清洁和消毒

Routine cleaning and disinfection of water points of use are recommended due to the amount of handling by personnel. The scope for cleaning and disinfection includes the exit points of use for purified water and Water for Injection (WFI) systems. The frequency and methodology for cleaning and disinfection should be based on the risk level for particulate and bioburden at the site adversely affecting the product to be manufactured. Two commonly used methods are as follows:

由于使用人员对使用水点经常手持操作，因此推荐对水点进行日常的清洁和消毒。范围包括纯化水和注射用水实用点出口位置。清洁和消毒的频次和方法应由位点上粒子和生物污染对所生产产品的污染的风险水平所确定。以下是两个常用的方法：

- Use of a thorough rinse of the dispensing head with the water from the water system at routine intervals as defined by approved standard operating procedures.
- 按照批准的标准操作规程，在规定的间隔时间，用该水系统中出来的水彻底冲洗的喷洒头冲洗；
- Spraying or wiping down the dispensing head with a sanitizer, disinfectant, or sporicide that has low carbon characteristics to prevent adversely affecting total organic carbon (TOC) testing. Examples of high-carbon products would be alcohol-based products. Low-carbon products would include hydrogen peroxide solutions without stabilizers. If a sanitizer, disinfectant, or sporicide is used that leaves a residue care must be taken to ensure that the residual is removed after decontamination.
- 用含碳较低的清洁剂，消毒剂或除孢子剂喷洒或擦拭喷洒头，以免影响TOC测试。高碳含量产品如酒精为基础的产品。低碳产品包含不含稳定剂的双氧水溶液。如果所用的清洁剂，消毒剂或除孢子剂会有残留，需确保在消毒后残留的去除。

For both chemical and bioburden testing, if the dispensing head to be sampled is a use point for manufacturing operations, it should be tested as it is used in the manufacturing process. That is, if a flush is required prior to use in operations, a flush should also be performed prior to sampling.

对于化学和生物负荷测试而言，如果需取样的喷洒头是用于生产的，它应该在生产过程中进行测试。也就是说，如果在生产过程中需要该使用点需要冲洗，则在取样前该冲洗动作应该先执行。

9.7 Disinfecting Drains 地漏的消毒

Drains should be limited to Grade C and Grade D areas. Drains should be capped, if possible, then opened for use and subsequently capped again. Routine disinfection of drains would provide very little success, as all surfaces of the drain's interior cannot be assured to be wetted by the antimicrobial chemical agent. Conversely, drains will most probably incorporate a biofilm on the inside of the drain that would prevent penetration of the disinfecting agent through the biofilm and from contacting the drain surface. Disinfecting the exterior of the drain's visible surface with sodium hypochlorite or peracetic acid and hydrogen peroxide may reduce bioburden, but such bioburden is expected to return within a short time period.

地漏仅限于C级和D级区域。地漏应该有盖子，如有可能，应仅在使用时打开，随后重新盖上。地漏的日常消毒作用很有限，因为其管道内表面不能保证被抗菌化学试剂完全湿润。相反，通常会在地漏下水管道内表面形成生物膜，制止了消毒剂的通过并于地漏表面接触。对于地漏的可见的外表面，可以用次氯酸钠、过氧乙酸和过氧化氢降低生物负荷，但这种生物负荷会在短时间内重新复原。

Firms should review local and municipal regulations regarding the use of or disposal of certain chemical agents through the sewer system.

企业应就使用或通过下水道系统处置化学剂的相关当地和市政条例进行审查。

Monitoring of drains itself may result in continually high results with no proactive corrective action that would be suitable. Monitoring directly on the drain or inside the drain should not be done.

监测排水系统可能会导致持续高的测试结果，并且没有可行有效的纠正措施。直接在排水系统内部进行监测也不恰当。

Monitoring points around the drain may provide information that is valuable to discern any possible adverse effect of bioburden that may be spread through the controlled area. However, setting of alert and action levels for such locations may prove to be without scientific value.

排水系统的监测点的设置应能有效辨别生物负荷可能会扩散到控制区域的不良事件。但是，这些区域的警戒限和行动限可能并没有科学价值

9.8 Reducing Corrosion and Deterioration of Surfaces 减少表面腐蚀和变质

The deterioration of surfaces that are routinely exposed to cleaners, sanitizers, disinfectants, and sporicides is a concern. Deterioration occurs for many reasons. Most notable are either a chemical reaction between the chemical agent and the surface substrate or the continual buildup of residues on the surface that deteriorate surfaces over time. Deterioration takes on several visible forms:

经常暴露于清洁剂，消毒剂，灭菌剂和除孢子剂的表面容易变质是一个需要关注的问题。变质的发生有很多原因。最显著的原因或者在于化学试剂之间的化学反应，表面残留的不停累积，使得经过一段时间后表面变质。变质的发生有以下几种形式：

- Corrosion: Corrosion is normally associated with metal surfaces and can take the form of rust or pitting. This deterioration is an attack of the impurities in the metal by the chemical agent (normal impurities in metals relate to carbon levels and purity of the metal grade, such as 304L stainless versus 316L stainless). This is normally seen with products containing chlorine.
- 腐蚀：腐蚀通常与金属材质表面有关，并且以锈蚀的形式发生。这种变质是金属中化学试剂对杂质的攻击（金属中的杂质水平通常与碳水平和金属纯度有关，如304L不锈钢VS 316L）。这些通常在含有氯的产品中可见。
- Chemical incompatibility with the surface: Chemical incompatibility with the surface normally occurs when the chemical agent reacts with the surface substrate and can deteriorate the surface via melting, softening, or

immediate discoloration. Such applications should be avoided. Incompatibility of the chemical agent with a substrate can be seen with peracetic acid and hydrogen peroxide compounds when used on softer and lower-grade metals as well as porous and nonporous substrates.

- 与表面不相容化学品：当化学试剂与表面物质发生反应时说明化学试剂与表面不相容，变质体现在融化，软化或直接变色。应该避免使用这种使用情况。这种化学试剂与基底的不相容性通常可见于过氧乙酸和氢气时使用柔软和低品位金属以及多孔和无孔基材的氧化化合物
- Drying: Drying of the surface substrate may occur with porous and nonporous soft substrates such as vinyl, Plexiglas, Kydex, Mipolam, and epoxy. This type of deterioration occurs as the chemical agent enters the pores or slight imperfections and over dries the surface. This is most notable with peracetic acid-hydrogen peroxide compounds, hydrogen peroxide compounds, or alcohols.
- 干燥：表面干燥的情况可能发生于多孔和无孔基质，如乙烯，有机玻璃，KYDEX，氯乙烯和丙烯腈的共聚物，和环氧树脂。这种类型的变质通常由化学试剂进入孔，轻微的缺口，然后使得表面过干。其中最明显的例子是过氧乙酸-过氧化氢化合物，过氧化氢化合物，或醇。
- Discoloring or staining: Discoloring or staining of the surface is normally due to dye in the cleaning agent that stains the surface. Staining or discoloring is normally seen with the use of phenols or iodine.
- 变色或染色：表面的变色或染色时清洁剂对表面的染色引起。变色或染色通常与酚类或碘的使用有关。

Surface deterioration is an avoidable occurrence and, with appropriate cleaning steps, can be reduced to minimum levels. Several precautionary steps can be taken to reduce the possibility of corrosion and subsequent deterioration. They are as follows:

表面的恶化可以通过使用合适的清洁步骤避免，或可以降低到最小水平。也可以采用一些预防措施也降低腐蚀的可能以及后续的恶化。比如：

- Careful evaluation of the chemical agent's active and inactive ingredients for compatibility with the surface substrates;
- 化学剂的活性和非活性成分与表面基材的相容性应仔细评估；
- Routine removal of residual buildup that may cause deterioration to the surface;
- 应例行清除可能导致地表恶化的残余堆积
- Careful evaluation for the mixing of agents or mixing of residuals on the surface
- 应对试剂在表面的混合或残留在表面的混合进行仔细评估；
- Prevention of overexposure of the surface to chemical agents;
- 防止表面对化学试剂的过度暴露；

9.9 Cleaning and Disinfection of Nonclassified Areas 清洁和消毒非洁净区域

Cleaning is not confined to environmentally classified areas. All buildings used in the manufacture, processing, packing, or holding of a drug product should be maintained in a clean and sanitary condition.

清洁并不仅限于有洁净级别的环境区域。所有生产，工艺过程，包装或产品的存储的区域都应该维持在一个干净和整洁的环境中。

Areas must be kept tidy and free of debris, and the introduction of materials into building areas that could impact classified areas should be evaluated to limit the introduction of bioburden, e.g. introduction of mold through wood pallets and corrugated cardboard. The building should be free of pests, and waste material should be held and disposed of in a timely and sanitary manner. The design of the areas within the building should enable thorough

cleaning, allowing all areas to be clean and orderly. There should be site policies to define the environmental classifications of all the areas and describe how they are maintained. Floors represent the highest level of contamination to the controlled environment and should be cleaned routinely with an efficacious nonsterile disinfecting agent.

区域应保持整洁，无碎屑，应对区域中引入对环境洁净有影响的物料进行评估，避免引入微生物，比如，霉菌可能通过木屑或波纹纸板引入。该建筑物应无病虫害，垃圾材料的处理应及时和卫生。建筑物内区域的设计应该方便有序清洁。应该有关于现场的政策来定义所有领域的环境分类，并描述他们如何保持。地板是受控环境的污染最高水平区域，应定期用有效无菌消毒液进行清洁。

10.0 Frequency For Cleaning And Disinfection

清洁和消毒频率

The selection of an appropriate cleaning and disinfection frequency for manufacturing facility surfaces (i.e., walls, ceilings, doors, non-product-contact equipment, surfaces, and floors) is essential for maintaining effective contamination control. The pharmaceutical and biotechnology industries have developed several approaches that have used one or more of the following criteria for selecting a frequency:

选择适当的生产厂房表面（如墙、天花板、门、非直接接触产品设备、表面以及地板）清洁和消毒频率对于维持有效的污染控制是至关重要的。医药和生物技术工业已开发了多种方法，采用下述一种或多种指标确定所用频率：

- Area Classification 区域洁净级别

Cleaning and disinfection frequencies based on area classification employ the most stringent cleaning and disinfection frequency for the most stringent area classification with a reduction in the cleaning and disinfection frequency as a function of reduced area classification. Based on this approach, a Grade A (ISO 5) location, for example, could be cleaned and disinfected daily, while Grade C (ISO 7) and Grade D (ISO 8) locations could be cleaned and disinfected weekly and monthly, respectively.

当基于洁净级别确定清洁和消毒频率时，洁净级别越高，清洁和消毒越频繁，而洁净级别降低时，清洁和消毒的频次也减少。例如，A级区（ISO5）每天清洁和消毒，而C级区（ISO7）和D级区（ISO8）可分别每周和每月清洁和消毒一次。

This approach is useful, but it does not take into account the risk of product contamination that may be associated with each manufacturing area or the type of manufacturing being conducted.

虽然该方法有些作用，但其没有考虑各个生产区域或生产活动类别所带来的产品污染风险。

- Environmental Monitoring (EM) Data 环境监控数据

The establishment of a cleaning and disinfection frequency based solely on EM data can result in a program that continually changes over time. This is due to potential fluctuations in the levels and types of bioburden recovered as revealed by daily or periodic data trending and review. This approach tends to be more reactive and retrospective in nature and has more typically been used to reduce established cleaning frequencies based on sustained satisfactory area performance.

仅仅依据环境监控数据来确定清洁和消毒频率，将使得监控计划随着时间不断变化。这是因为每天或定期数据趋势分析所展示的生物负载水平、类别可能都在变动。所以该方法本质上是被动和回顾性的，通常用来支持减少那些监控结果持续符合区域的清洁频率。

- Risk-Based Model 基于风险的模型

This approach employs elements of the preceding two approaches but also takes into account the risk of product exposure to the environment and personnel and the type of manufacturing conducted in the classified area.

该方法采用上述两种方法的要素，同时考虑了产品暴露对环境和人员带来的风险，以及该区域内所进行生产活动类别。

Several principles can be used to help define a risk-based cleaning and disinfection frequency for classified areas:

以下原则可用于确定洁净区基于风险的清洁和消毒频率：

- The cleaning and disinfection frequency of classified areas should be commensurate with the associated risks of product contamination or cross contamination. Therefore, the open versus closed nature of the process, potential exposure to personnel, and the stage of the process with respect to the final sterilization step (where applicable) should be the primary criteria for selecting a cleaning and disinfection frequency. To minimize the risk of product contamination whenever possible operations should be closed.
- 洁净区清洁和消毒频率应与产品污染或交叉污染的风险相适应。因此，是开放还是密闭工艺、人员暴露可能、适当时所处的工艺步骤（相对于最终灭菌工序），都应作为选择清洁和消毒频次的基本标准。为了尽可能降低产品污染风险，应尽量采用密闭工艺。
- Those classified areas within an aseptic manufacturing boundary (for example, Grade D to Grade C) should be cleaned and disinfected more frequently than those areas outside the boundary.
- 无菌生产厂房内的洁净区（例如，D级区至C级区）的清洁和消毒应比其他同级别区域更频繁。
- ISO 8 manufacturing areas that are immediately adjacent and contiguous (via airlocks) with open aseptic processing areas (for example, Grade C and adjacent Grade A) may require more frequent cleaning and disinfection than those Grade D areas not immediately adjacent and contiguous with such areas (such as a Grade D area adjacent to a Grade C area versus an independent and separate Grade D manufacturing area or suite supporting closed-system processing).
- 与开放的无菌操作区（如C级区和相邻A级区）直接相邻和连接（通过气闸间）的ISO8生产区，可能比那些非直接相邻和连接的D级区需要更高的清洁频率（如与C级区相邻的D级区相对于独立的D级区或密闭系统D级辅助区）。
- The cleaning and disinfection of manufacturing areas should be conducted for each product changeover per established procedures to reduce the risk of cross contamination.
- 应按照批准的程序，在每次更换品种时进行生产区域的清洁和消毒，以降低交叉污染的风险。
- Areas and surfaces that can serve as a vehicle for microbial ingress into the classified area or that may support microbial growth may require cleaning and disinfection at a greater frequency than other areas or surface locations. Ingress areas include gowning entry airlocks, doors, and floors.
- 可能成为微生物侵入洁净区的工具或者可能利于微生物生长的区域和表面，其清洁和消毒频率应高于其他区域或表面。如更衣气闸间、门和地板。
- Areas that support microbial growth include locations for charging of powdered media and/or ingredients to vessels.
- 利于微生物繁殖的区域包括粉末性培养基和/或成分投料点。
- Selected facility design issues, such as the age of the building or a difficult-to-clean layout, may warrant an increased cleaning and disinfection frequency.
- 厂房设计如建筑物的年龄或难以清洁的布局设计，都要求更高的清洁和消毒频率。
- Selected events may warrant additional cleaning and disinfection beyond the routine frequency. Examples may include microbial air or surface action level excursions, power and/or HEPA filter failures, or periodic facility shutdowns.
- 特定事件可能要求进行额外的清洁和消毒。例如浮游菌或表面菌监控超出行动限、停电和/或HEPA过滤器故障或厂房的定期关闭。
- The cleaning and disinfection frequency selected for any classified area must be supported by ongoing

satisfactory EM data. Frequent review of the environmental data should be conducted to evaluate the cleaning and disinfection efficacy. Based on the review, the cleaning and disinfection frequency for the area may warrant modification to ensure an area can meet and maintain established monitoring levels.

- 任何洁净区的清洁和消毒频率必须有持续的合格环境监控数据来支持。应经常回顾环境监控数据，评估清洁和消毒效率。根据回顾结果，可能需要调整该区域的清洁和消毒频率，保证该区域符合并维持在适当的监控水平。

An example of a risk-based approach for selecting a routine cleaning and disinfection frequency is provided in Figure 10.0-1. Example risk levels for varying types of manufacturing processes and area classifications are provided. Based on the risk level and the manufacturing type, example cleaning and disinfection frequencies are listed. The figure illustrates the risk-based approach in that different manufacturing areas with the same area classification may have different cleaning and disinfection frequencies due to the risk of product contamination from the environment, human exposure, and the type of manufacturing performed in the area. (Note that additional controls may apply for the examples presented in the figure.).

基于风险的方法确定日常清洁和消毒频率的示例见图10.0-1。该图提供了不同类别的生产工艺和洁净级别的风险等级。根据风险等级、生产类别，列出了相应的清洁和消毒频率。该图表明，因为环境对产品污染的风险、人员暴露以及生产活动类型不同，具有相同洁净级别的不同生产区域的清洁和消毒频率可能不同。（注意：图中展示的示例可能还需要额外的控制措施）。

In summary, multiple approaches have been used successfully within the industry to select an appropriate cleaning and disinfection frequency for classified areas that result in contamination control, as evidenced by satisfactory EM data. However, an approach based on the risk of product contamination due to its exposure to the environment, personnel, and the manufacturing process itself provides the greatest flexibility and the opportunity to tailor the contamination control and disinfection program to the particular facility design, area use, and manufacturing risks.

总之，不同方法均已成功用于洁净区清洁和消毒频率的选择，环境监控数据证明污染得到有效控制。但是，基于产品暴露于环境、人员以及生产工艺本身带来的产品风险的方法，提供了最大的灵活性，以及根据特定厂房设计、使用和生产操作风险来调整污染控制和消毒计划的机会。

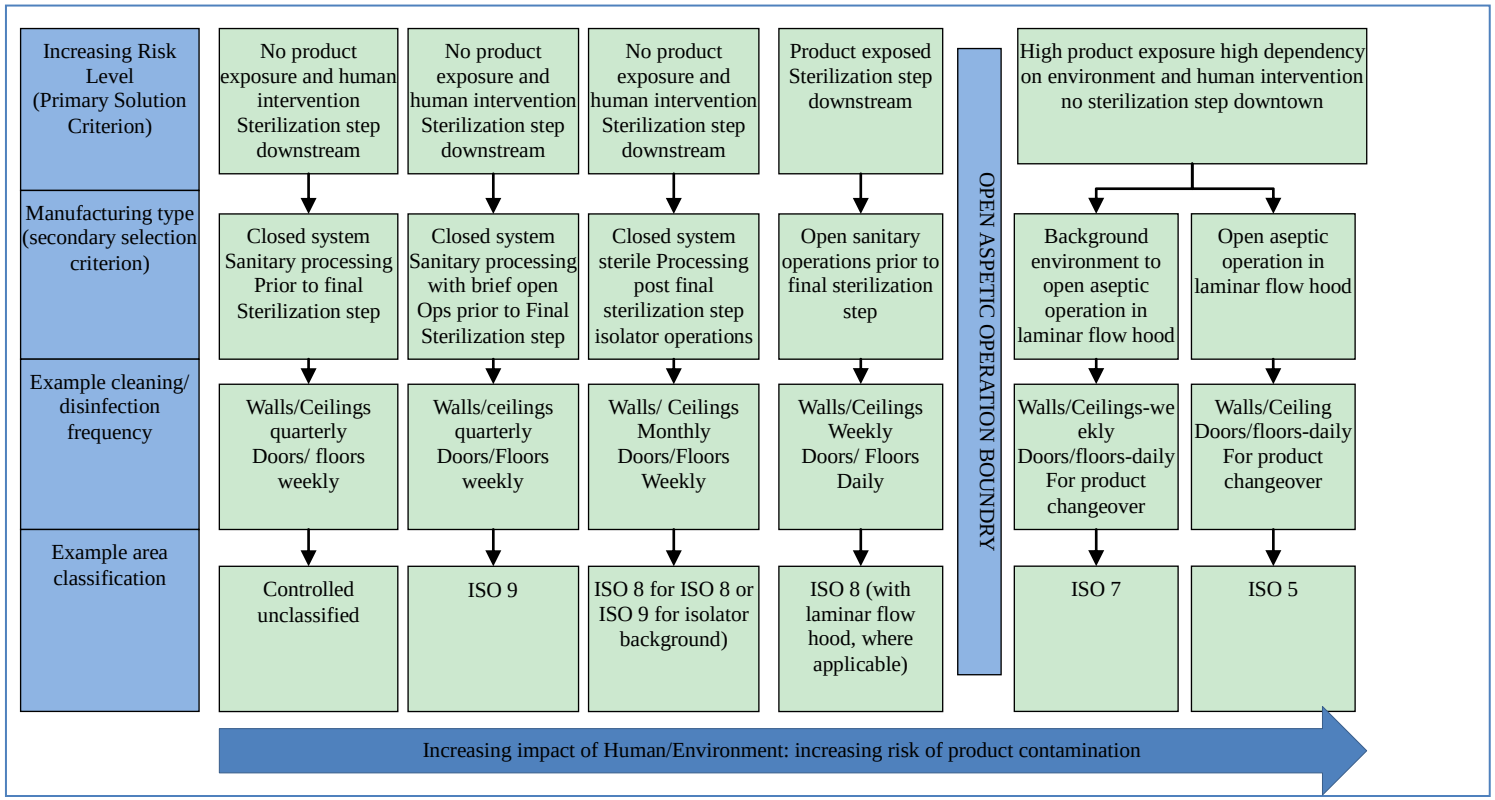

Figure 10.0-1 Example Risk-Based Approach for selection of Routine Cleaning and Disinfection Frequencies for Classified Manufacturing Areas

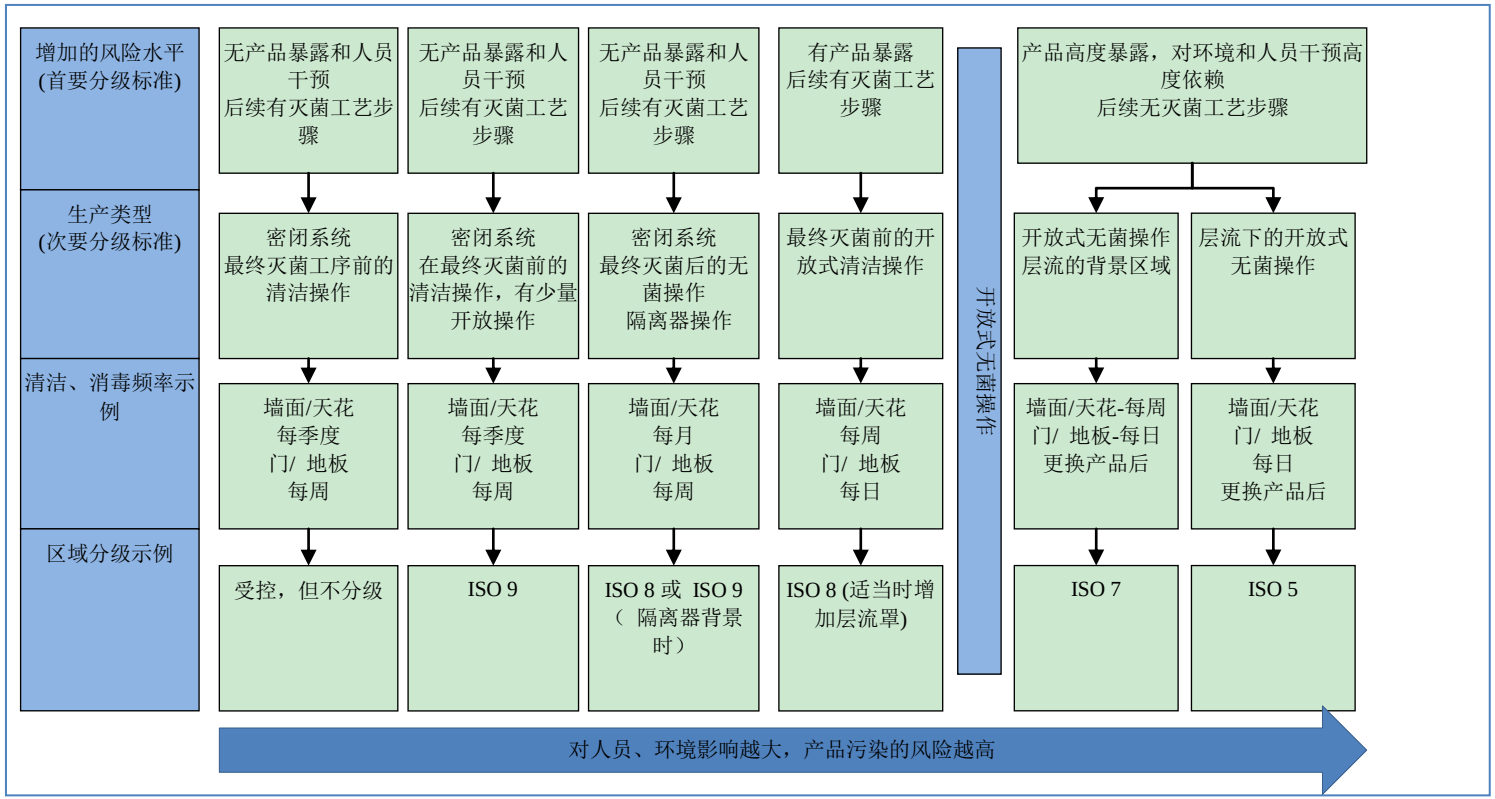

Figure 10.0-1 各级别生产区域日常清洁和消毒频率-基于风险的选择方法示例

11.0 Resistance and Rotation 耐受和轮换

For many years there has been a great debate on the subject of the possible development of resistance of microorganisms to sanitizers, disinfectants, and sporicides. Concerns for the possible resistance of organisms to these products are based on a theoretical relationship to resistance found with antibiotics.

对于微生物可能对清洁剂、消毒剂和杀孢子剂产生耐受性，多年来存在较大争议。担心微生物可能对这些产品产生耐受性是基于其对抗生素出现耐受的理论关系上。

To date, there is no conclusive published test data proving such development of resistance by organisms to these agents. Resistance to antibiotics is usually acquired through modification of a single gene (or acquisition of a single gene) that blocks the very specific action of the antibiotic. The antimicrobial agents typically employed in clean rooms continue to be effective because they have numerous effects on a number of aspects of cellular physiology. This means that multiple mutations would be required in a short period of time (e.g., five-minute contact time) with exposure to low numbers of cells typically found in a clean room to overcome their detrimental effects. As such, resistance of a cell to agents used in the disinfection process would be highly unlikely given the environmental conditions and low cell numbers.

迄今为止，尚没有已发表的结论性试验资料来证明微生物对这些产品产生耐受。对抗生素的耐受通常是通过对一个单一基因的修饰获得的（或获得一个单一的基因），从而阻断了抗生素的特定作用。洁净室中使用的抗微生物试剂持续有效，因为其对一系列细胞生理活性具有多种作用。这意味着洁净室发现的少量微生物需在较短时间内（如5分钟接触时间）完成多次突变，以克服抗微生物试剂的不利作用。因此，考虑到环境因素和较低的微生物数量，微生物对消毒使用的试剂产生耐受性是极不可能的。

This is also supported by the current USP <1072> Disinfectants and Antiseptics *(9):*

USP <1072>消毒剂和防腐剂（9）也支持这一观点：

The development of microbial resistance to antibiotics is a well-described phenomenon. The development of microbial resistance is less likely, as disinfectants are more powerful biocidal agents than antibiotics and are applied in high concentrations against low populations of microorganisms, so the selective pressure for the development of resistance is less profound.

微生物对抗生素产生耐受是一常见现象。而对消毒剂产生耐受则不太可能，因为消毒剂比抗生素有更强的杀灭作用，且相对于少量的微生物使用了高浓度的消毒剂，

Based on this, the pharmaceutical and biotechnology industries have moved away from the rotation of two disinfecting agents. This formerly common practice led to high residue levels and subordinate efficacy performance. Today, most firms use a system whereby a disinfectant is rotated with a sporicide to more effectively reduce the bioburden levels. The rotation of a disinfectant with a sporicide is superior to the rotation of multiple disinfectants. If desired, the sole use of a sporicidal product that has proven efficacy can be implemented without a rotation. If used on a routine basis, the sporicide should destroy the level of contamination necessary to assure acceptable environmental conditions.

因此，药品和生物技术企业已不再恪守两种消毒剂轮换的做法。这种早期普遍接受的做法导致残留水平过高，并且忽视了实际消毒效果。如今多数公司采用一种消毒剂和一种杀孢子剂轮换的系统，以更有效地降低微生物负载。这种轮换要优于多种消毒剂的轮换。必要时，可仅采用已证实有效的一种杀孢子剂，而不进行轮换。如果定期使用，则可破坏污染水平确保达到适当的环境要求。

However, the use of sporicidal agents alone is discouraged due to their inherent corrosive nature.

然而，由于杀孢子剂固有的腐蚀性，并不鼓励只使用杀孢子剂。

All rotation systems should be evaluated via the use of area classification, environmental monitoring data, and/or risk assessment.

所有轮换系统都应依据区域分级、环境监控数据和/或风险评估进行合理评价。

12.0 Return From a Shutdown

停产后恢复至生产状态

A shutdown is a planned or required stoppage of operations that is likely to compromise the environmental conditions in the classified area. A shutdown can occur because of regularly scheduled activities such as preventive maintenance and construction activities or because of unscheduled activities such as unexpected power outages. The extent and duration of the shutdown can result in varying levels of viable and nonviable contamination being introduced to the area or facility. Actions must be taken following a planned or unplanned shutdown to bring the area or facility back to a state of control in accordance with the area's environmental classification.

停产指计划性或需要停止生产操作，并可能破坏洁净区环境。停产可能因为定期有计划的活动如预防性维护和建造活动，或者因为无计划的活动如非预期的停电。停产的程度和维持的时间会导致洁净区或厂房的不同水平的活性和非活性污染。计划性或非计划性停产后必须采取行动以将洁净区或厂房恢复至相应洁净级别的受控状态

Criteria for returning the facility to a state of control after a shutdown should include verification that all control systems, such as air handlers, are functioning properly. Prior to disinfection, cleaning with detergent or water should be performed first to remove dirt left from construction or other shutdown activities. After cleaning, disinfection should be performed in accordance with established procedures to reduce the bioburden to acceptable levels. All surfaces, including walls, floors, and equipment surfaces, should be included in the disinfection process. When possible, the cleaning and disinfection process should be supported with in-situ data to demonstrate that the multistep cleaning and disinfection regimen employed and the types of antimicrobial chemical agents used are qualified to bring the facility back to a state of control.

停产后将厂房恢复至受控状态的标准应包括确认所有控制系统，如空气处理器正常运行。在消毒前，用消毒剂或水先去除建造或其他停产活动导致的污物。清洁后，按照既定程序消毒降低生物负载至合格水平。所有表面，包括墙、地面和设备表面，都应进行消毒。可能时，清洁和消毒程序应有数据支持，以证明各清洁和消毒方案和抗微生物试剂类别已经确认，能够将厂房恢复至受控状态。

After cleaning and disinfection is complete, and before normal operations resume, the area should be monitored for viable and nonviable particulates. If possible, the monitoring data should be evaluated to verify the area is back within a state of control before it is returned to use.

清洁和消毒结束后，正式生产开始前，应监控洁净区的微生物和尘埃粒子。可能时，应评估监控数据，以确认洁净区使用前恢复至受控状态。

13.0 Hold Times For Cleaned Areas,Non-Product-Contact Equipment, and Utensils 洁净区、非产品接触设备和器具的保持时间

After an area or facility has been cleaned and disinfected, studies should be performed to establish a maximum time period between cleaning and disinfection in the absence of production activities.

洁净区或厂房清洁和消毒后，应进行研究以建立未进行生产时清洁和消毒之间最大的时间间隔。

Studies should be based on viable and nonviable sampling performed after cleaning and disinfection and at or beyond the maximum time allowed between cleaning and sanitization. Entrance into the area after cleaning should be limited. The study should include the normal level of nonproduction activities that would occur in the area.

该研究应基于清洁和消毒后以及清洁和消毒最大允许时间或之后的微生物和尘埃粒子取样。应限制人员清洁后进入该区域。该研究应包括区域内可能发生的正常量的非生产性活动。

Hold times for non-product-contact equipment and utensils should be established and validated.

应建立非产品接触设备和器具的保留时间，并进行验证。

Those materials should be stored in a manner that ensures integrity is maintained for the established hold times. If hold times are exceeded for areas, non-product-contact equipment, or utensils, they need to be cleaned and disinfected again.

应保留这些材料为已建立的保持时间提供支持。如果超出了洁净区、非产品接触设备或器具的保持时间，应重新进行清洁和消毒。

14.0 Training 培训

Personnel need to be properly trained on the standard operating procedures that govern the program as well as the specific cleaning and disinfection techniques used. This training should be documented and re-administered periodically. It is important that both the individuals performing the cleaning and disinfection activities and their supervisors be trained.

人员应经过适当的相关操作程序及清洁和消毒技术的培训。培训应有记录，并定期进行。重要的是进行清洁和消毒操作的人员及其主管都应接受培训。

As many of the cleaning and disinfection processes are manual in nature and their outcome (contamination reduction) dependent on execution, the level of training and general understanding of the process becomes a critical factor in implementing a successful cleaning and disinfection program. While it is clear that training on the SOPs that govern the cleaning and disinfection program is required, additional general training should also be developed to ensure the appropriate level of underlying knowledge is present.

本质上许多清洁和消毒程序都是手工进行，所以其输出（降低污染）取决于执行情况，培训的水平和对工艺的基本认识是成功完成清洁和消毒方案的重要因素。很明显必须进行清洁和消毒相关SOP培训，还应开发额外的培训进行基础知识的培训。

The scope of the training should encompass but not necessarily be limited to the following aspects, which will be discussed in more detail:

培训的范围应包含但不限于以下方面，后续将进一步予以讨论：

- Basic microbiology
- 基础微生物学
- Basic environmental monitoring
- 环境监控基本知识
- Contamination sources and risks
- 污染来源及风险
- Aspects of a cleaning program
- 清洁方案的内容
- Facility design and airflow
- 厂房设计和气流组织
- Aspects of a disinfection program
- 消毒方案的内容
- Gowning • Relevant SOPs
- 更衣相关SOP
- Clean room behavior and personal hygiene

- 洁净室行为规范和人员卫生
- Assessment of understanding
- 对以上内容理解的评估

For personnel to be able to do the best job in cleaning and disinfection, they should have a basic understanding of the total framework of where they need to carry out their work. Once the framework in which they have to operate is better understood and they are supplied with the right tools, they should be able to perform their jobs at the required level of proficiency.

为了更好地完成清洁和消毒工作，人员应对其所需完成工作的整个架构有个基础的理解。一旦有了更好的理解，并为其提供正确的工具，他们将能够熟练地完成自己的工作。

14.1 Basic Microbiology 基础微生物学

The aim of disinfection is to destroy viable microorganisms in the clean room. It is therefore important that operators and cleaning staff understand what organisms may be present, how they are multiplying, how they are recovered, and the mechanism by which they are destroyed. Topics that staff needs to understand at the end of the training include but are not limited to:

消毒的目的是杀死洁净室中活的微生物。因此重要的是操作者和清洁人员理解可能存在哪些微生物，它们是如何繁殖、恢复以及杀灭机制。培训后员工需要理解的内容包括但不限于：

- The type of viable microorganisms that exist in clean rooms
- 洁净室中存在的活微生物的类别
- How microorganisms multiply and what is needed for multiplication
- 微生物如何繁殖，以及繁殖条件
- The difference between vegetative organisms and spores
- 有生长能力的微生物与孢子之间的区别
- The mechanism by which vegetative organisms and spores are destroyed
- 有生长能力的微生物和孢子的杀灭机制
- Methods used to detect their presence
- 检测其是否存在的方法
- The definition of a colony-forming unit (CFU)
- 菌落形成单位的定义
- How microorganisms can compromise final product (safety, purity, and potency) if not minimized
- 如果不降低微生物数，它们是如何影响最终产品的（安全、纯度和效价）
- Endotoxin and methods used for its reduction
- 内毒素以及降低内毒素的方法

14.2 Contamination Sources and Risks 污染来源和风险

For operators or cleaning staff to perform their cleaning and disinfection tasks appropriately, they need to understand where contamination might come from, how it enters the clean room, and what the risks are if the

contaminants are not addressed properly. At the end of the training they need to be able to identify the following as possible sources of contamination:

为了适当的完成清洁和消毒工作，操作者或清洁人员需要理解污染来自哪里，它如何进入洁净室，如果没有适当处理会带来什么风险。培训后他们应能够识别以下可能额污染源：

- People 人员
- Air 空气
- Mobile equipment 移动设备
- Water 水
- Fixed equipment 固定设备
- Cleaning supplies 清洁用物品
- The process being performed 所进行的操作

14.3 Facility Design and Airflow 厂房设计和气流组织

Principles of "first air" and aseptic techniques should, of course, be well understood by operators and the cleaning staff. They should understand how filtration (specifically, HEPA filtration) and airflow are used to remove contaminants. Personnel also need to identify high-risk zones. Topics they need to understand at the end of the training include but are not limited to:

操作者和清洁人员应能很好地理解“空气第一”和无菌技术的基本原理。他们应理解如何使用过滤（尤其是HEPA过滤）和气流组织来去除污染的。员工也需要识别高风险区域。培训后他们需要理解的内容包括但不限于：

- Basic HVAC design and HEPA filtration principles, including the purpose of unidirectional airflow
- HVAC设计基础和HEPA过滤原理，包括单向流的使用目的
- Facility surfaces and how to clean them appropriately
- 厂房表面，以及如何进行适当清洁
- The role of airflow in contamination containment and how smoke studies are used to visualize it
- 气流组织在污染防控中的作用，以及如何用烟雾试验来确认
- High-risk zones in regards to introduction of contamination
- 污染引入的相关高风险区

14.4 Gowning 更衣

The cleaning staff will contribute to the level of bioburden in a clean room. As an added risk, physical labor may result in increased perspiration, which may increase contamination emitted by personnel and may compromise the gowning barrier efficiency. Topics cleaning staff need to understand at the end of the training include but are not limited to:

清洁人员会提高洁净室中生物负载的水平。作为一种额外风险，体力劳动可能导致出汗增多，这可能导致人员带来污染的增加，并可能破坏服装屏障的有效性。培训后清洁人员需理解的内容包括但不限于：

- The importance of gowning in the clean room environment

- 洁净室中更衣的重要性
- Human factors that influence the ability of the gown to provide the level of protection needed
- 人员因素对更衣保护功能的影响
- How the gown barrier optimally functions
- 服装屏障如何更好地发挥作用
- Basic principles of gowning (gown, head cover, beard cover, glasses, gloves) to prevent materials contamination
- 通过更衣（衣服、头套、胡须套、眼镜、手套）防止物料污染的基本原则
- Liquids and their impact on gowning materials
- 液体以及其对更衣物料的影响

14.5 Clean Room Behavior and Personal Hygiene 洁净室行为规范和人员卫生

All people entering a clean room should understand what is expected of them with regards to personal hygiene. Topics trainees need to understand at the end of the training include but are not limited to:

进入洁净室的所有人员都应理解对其人员卫生方面的要求。培训后其需要理解的内容包括但不限于：

- The importance and components of appropriate personal hygiene
- 适当人员卫生的重要性及其组成
- The impact of dry skin on shedding
- 皮肤干燥对脱落物的影响
- Proper washing and sanitization of the hands
- 手部的适当清洗和消毒
- Appropriate movement within a clean room
- 适当的洁净室内走动
- Appropriate handling of materials, cleaning supplies, surfaces, and equipment
- 物料、清洁用品、表面和设备的适当处理

14.6 Basic Environmental Monitoring 环境监控基础

Individuals involved with cleaning and disinfection should understand why environmental monitoring samples are taken and how the data is used. Topics they need to understand at the end of the training include but are not limited to:

参与清洁和消毒的人员应为何取样进行环境监控，以及如何利用这些数据。培训结束后他们需要理解的内容包括但不限于：

- What an EM sample is and how it is taken
- 何为环境监控样品，以及如何取样
- How EM data are used to evaluate the performance of the cleaning and disinfection program
- 如何利用环境监控数据评价清洁和消毒方案的效果
- How EM can help cleaning staff or operators improve their job performance

- 环境监控如何帮助清洁人员或操作者提高其工作绩效
- What the limitations of EM reporting are
- 环境监控报告的局限性是什么
- How an evaluation of the EM data is used in understanding whether the product was manufactured under the appropriate environment
- 如何利用环境监控数据评估结果来确定产品在适当环境下生产

For detailed information on environmental monitoring see PDA Technical Report 13: *Fundamentals of an Environmental Monitoring Program (13).*

关于环境监控的更多信息，参见PDA技术报告13：环境监控基础

14.7 Aspects of a Cleaning Program 清洁方案的各个方面

Personnel need to understand that cleaning is a separate operation from disinfection and that dirtied surfaces can sometimes complicate disinfection. Topics they need to understand at the end of the training include but are not limited to:

人员需理解清洁相对于消毒是个独立的操作，脏的表面有时能使消毒更为复杂。培训后他们需要理解的内容包括但不限于：

- What the term *dirty surface* means in our industry
- 行业中脏的表面意味着什么
- What the typical types of dirt are in our industry (product residue, antimicrobial chemical agent residue, organic or inorganic material, etc.)
- 行业中典型的污染类型（产品残留、抗微生物化学试剂残留、有机或无机物质，等）是什么
- What the difference is between cleaning and disinfecting
- 清洁和消毒的区别是什么
- What the general approaches used for cleaning are
- 通用的清洁程序是什么
- How cleaning agents are prepared
- 如何制备清洁剂
- How cleaning tools are used
- 如何使用清洁器具
- How to handle the cleaning agents from a safety point of view
- 从安全的角度如何处理清洁剂
- How to approach the cleaning of: 如何清洁
  - Walls 墙面
  - Carts and furniture 转移车和器具
  - Ceilings [outside of Grade A (ISO 5) areas] 天花板（A级区域之外的）

- Equipment and machinery 设备
- Floors 地板
- Curtains and barriers 围帘和隔断

14.8 Aspects of a Disinfection Program 消毒方案的各个方面

Although the people involved in the cleaning and disinfection of clean rooms are normally not involved in validation, they should understand why certain antimicrobial chemical agents are chosen for specific surfaces and how validation or qualification is performed. The training should also focus on how to apply the agents correctly and how to remove residues on critical surfaces. Topics they need to understand at the end of the training include but are not limited to:

尽管参与洁净室清洁和消毒的人员通常不参与验证，他们应理解特定表面为何选用某些抗微生物试剂，以及如何进行验证或确认。培训重点是如何正确使用这些试剂，以及如何去除关键表面的残留物。培训结束后他们需要理解的内容包括但不限于：

- Which antimicrobial chemical agents are used for disinfection
- 使用何种抗微生物试剂进行消毒
- How antimicrobial chemicals work
- 抗微生物试剂的作用
- How antimicrobial chemical agents used in disinfection are chosen and qualified
- 如何选择消毒用的抗微生物试剂，如何进行确认
- What a residue is and how it is removed
- 什么是残留，如何去除
- How to prepare the antimicrobial chemical agent and how to make the correct dilutions
- 如何制备抗微生物试剂，如何正确地稀释
- What the goal is with each disinfection step
- 每一消毒步骤的目的是什么
- What surfaces should be disinfected
- 哪些表面需要消毒
- What the limitations of disinfection are
- 消毒的局限性是什么
- How to correctly apply and remove antimicrobial chemical agents
- 如何正确使用并去除抗微生物试剂
- The how and why of "back to front" mopping techniques
- 如何完成“从后至前”擦拭技术，为何采用这种方法
- How to disinfect, using what tools where
- 如何进行消毒，哪些地方采用何种器具

- Room hold time before entering the clean room
- 进入洁净室前房间的保持时间
- How to clean the disinfecting tools
- 如何清洁消毒工具
- How to handle the antimicrobial chemical agent from a safety point of view
- 从安全的角度，如何正确处理抗微生物试剂
- Room hold time after disinfection and before entering the clean room again for disinfection
- 消毒后至进入洁净室进行消毒前的保持时间
- Contact time for disinfection
- 消毒剂的接触时间
- How EM results help identify areas where the disinfection program may need to be modified
- 如何利用环境监控数据识别哪些区域的消毒计划需要修订

14.9 Assessment of Understanding and Qualification 培训效果评估和资质确认

Effective training evaluates what trainees understand before training begins and again after training has completed to assess what was retained. Assessing prior knowledge may be useful in the development of the appropriate course material. Post-evaluations indicate the effectiveness of the training.

有效的培训应评价培训前后受训者掌握的内容，以评估其学习效果。评估以前的知识有助于建立适当的培训教材。而培训后评价则说明了培训效果如何。

Post-assessments are critical as the trainee is now performing procedures from training on a daily basis. Assessments should be rendered by supervisory personnel of the individual performing such capacities. At the end of the training, all aspects of that training should be assessed, measuring the level of understanding with respect to what has been discussed. Based on the outcome, further training may be deemed necessary.

培训后评估十分关键，因为受训者按照培训的程序进行日常操作。评估应由进行操作人员的主管进行。培训后，应对培训进行全面的评估，判断其对培训内容的理解程度。根据评估结果，可能需要进行进一步的培训。

15.0 Conducting Investigations Related To Cleaning And Disinfection

执行与清洗和消毒相关的调查

Cleaning and disinfection programs and practices that are not followed can result in unacceptable microbial levels in areas or on equipment within the facility. Investigation related to negative shifts, excursions, or trends in the EM data should include a review of the cleaning and disinfection program.

不遵循清洗和消毒程序和规程可导致厂房内的区域或设备上的微生物限度超标。有关环境监测数据的负面变化、短时偏移或趋势的调查应包括对清洗和消毒程序的审核。

For investigations related to viable contamination, the type of organism can be an important factor in understanding the possible source. The following list offers three organism types and common sources:

对于有关活菌污染的调查，微生物的类型可以是了解可能来源的重要因素，下面列表提供了3个微生物类型和常见来源：

- **Gram-positive cocci and small non-spore-forming gram-positive rods**
- **革兰氏阳性球菌和小型无芽孢革兰氏阳性杆菌**

The most prevalent contamination source is personnel.

最普遍的污染源是人员。

- **Gram-positive rods and fungi**
- **革兰氏阳性杆菌和真菌**

The most prevalent contamination source is the external environment (air and soil), which can include the facility's interstitial spaces.

最普遍的污染源是外部环境（空气和泥土），包括厂房的间隙空间。

- **Gram-negative rods**
- **革兰氏阴性杆菌**

The most prevalent contamination source is water or liquid related.

最普遍的污染源是水或液体相关的。

When reviewing the cleaning and disinfection program as part of an investigation, areas that should be considered based on the data available include but are not limited to:

当审核清洗和消毒程序作为调查的一部分，根据可获得的数据应该考虑的方面包括但不限于：

- Antimicrobial chemical agent residue buildup and soil that have not been adequately removed by cleaning, thus preventing adequate disinfection
- 通过清洗未完全去除的抗微生物化学试剂残留积聚和泥土，因此妨碍了充分的消毒
- Inappropriate application of antimicrobial chemical agents
- 抗微生物化学试剂使用不当
- Insufficient contact times on surfaces

- 与表面接触时间不够
- Inappropriate decontamination of components or bagging before transfer to the controlled area
- 在进入受控区域前未正解地对组份或包装净化
- Use of inadequate clean room- tools
- 使用不适当的洁净区工具
- High bioburden or shedding from inappropriate cleaning apparatus
- 高生物负荷或不当清洗设备的脱落物
- Expired solution
- 过期溶液
- Incorrect selection of agents in relation to the organisms found
- 相对于所发现的微生物试剂选择不当
- Incorrectly prepared solutions
- 溶液制备不当
- Lack of adherence to established cleaning and disinfection procedures
- 未遵守已建立的清洗和消毒规程

The following questions may be helpful to ask during an investigation based on the area of focus:

根据所关注的区域在调查中下列问题可以帮助询问：

Equipment Related

设备相关

- For area disinfection (floors, walls, countertops), is the disinfection equipment clean and dry before each use? If it is a Grade A/B (ISO 5/6) area, is the equipment, including tanks and tubing, sterilized before each use?
- 对于消毒区域（地板、墙面、工作台面），每次使用前消毒设备清洗和干燥了吗？如果是A/B（ISO 5/6）区，设备包括贮罐和管路每次使用前已灭菌了吗？
- Is the equipment stored properly in a clean area and covered until use?
- 设备在洁净区存放是否适当且使用前是否覆盖？
- For transfer disinfection, are spray containers either single use or properly cleaned before reuse?
- 对于扩散式消毒，喷洒容器是一次性使用还是再次使用前适当清洗？
- Are carts used for transport properly disinfected, including the wheels?
- 用于运输的小推车包括车轮是否经过适当消毒。

Materials and Solutions Related

物料和溶液相关

- Is cleaning and disinfection performed starting from the cleanest area and progressing to the dirtiest area?
- 清洗和消毒是否从最洁净区域开始进而到最不洁净区域？
- Are disinfection efficacy studies available at the site to include methods and expiry dating, as well as any

predominant site isolates?

- 在该场所是否有消毒效力研究包括方法和失效日期以及是否有隔离的主要地点？
- Are antimicrobial chemical agents adequately rotated with the use of a sporicide to maintain low levels of spore-forming organisms without causing erosion of surfaces from overuse?
- 循环使用的杀孢子剂类抗微生物化学试剂是否足够以维持产孢子微生物在低水平且不至于过度使用而使表面侵蚀？
- Is the antimicrobial chemical agent applied such that the surfaces remain wet for the required or validated contact time, yet are not overly wet so as to cause puddles to remain, which may allow non-fermenting gram-negative organisms to proliferate?
- 是否所用的抗微生物化学试剂对于所需要或验证的接触时间会导致表面保持潮湿？或虽没有过度潮湿但有水洼残存从而可能使非发酵革兰氏限性微生物得到增殖？
- Are the site procedures clear on how to apply antimicrobial chemical agents and designated contact times for each agent?
- 厂地的规程是否清晰说明如何使用抗微生物化学试剂并指定了每个试剂的接触时间？
- Are in-situ studies available that demonstrate effectiveness of the site's restart disinfection program for activities such as after construction, after a power outage, or after prolonged shutdown of an area?
- 现场是否有研究证实某区域在施工、停电或长期停工后厂地重新消毒规程的有效性？
- Do the certificates of analysis on the antimicrobial chemical agents used show any changes?
- 分析报告书是否显示所用的抗微生物化学试剂有任何的变化？
- If the antimicrobial chemical agent is not purchased sterile and is sterile filtered in house, do the records from the sterile filtration process as well as bioburden data available reveal any issues?
- 所购买的抗微生物化学试剂是否不是无菌的？是否企业内部过滤，无菌过滤工艺的记录以及可用的生物负荷数据是否显示任何问题？

Personnel/Training

人员/培训

- Are accurate and complete SOPs in place and available?
- 有准确和完整的SOP且可以获得吗？
- Are operators trained and qualified on how to apply the antimicrobial chemical agent, including contact time and removal of residuals where applicable?
- 操作者经过培训并考核合格知道如何应用抗微生物化学试剂，包括接触时间以及如何去除残留吗？
- Have the antimicrobial chemical agents been prepared properly?
- 抗微生物化学试剂制备合适吗？
- Are personnel instructed not to enter areas that have been disinfected until after the contact time has been exceeded?
- 人员是否经过指示在超过接触时间前不要进入消毒区域？
- Are areas of construction properly segregated from in-services areas to prevent cross contamination? Are there

additional precautions and disinfection and cleaning activities for personnel in the transition areas?

- 建筑物区域是否与服务区适当隔离以避免交叉污染?过滤区域的人员有没有额外的预防、消毒和清洗活动？
- Are clean room staff trained in and exhibiting consistently good aseptic technique?
- 洁净区人员经培训具有并表现出一贯地良好无菌操作技术吗？

Additional information on investigating environmental monitoring excursions can be found in PDA *Technical Report No. 13 (Revised 2014): Fundamentals of an Environmental Monitoring Program (13).*

有关环境监测短时超限的调查的额外信息可以见*PDA技术报告13（2014年修订本）：环境监测程序的基本原则（13）*。

16.0 Conclusion 结论

A robust contamination control system starts with controlling contamination from entering classified areas. Such a system stages items from the exterior environment to be cleaned, disinfected and sterilized prior to entry. Without a system for controlling contamination from entering the loss of control for the environmental conditions is very likely. Cleaning compliments the control system as the blockage of all contamination from entering is extremely difficult. Cleaning with a non-abrasive type action and subsequent lifting of dirtied soils, liquids, particulates and microbes prepares the surface to be characteristically lower in soil/residue and bioburden making disinfection of what remains a simpler and more successful process. The disinfection of areas utilizing a validated agent is done correct the errors that have occurred during the control and cleaning process. Cleaning and disinfection of classified areas is not a preventative measure but rather a corrective action procedure done to equalize the failures of the control system. Many pertinent details defined in this technical report combine together to help provide the opportunity for success which is measured as consistent acceptable environmental conditions. Consistent control is the ultimate goal. This technical report is not intended to replace any existing requirements or standards, it is a best practice reference documents regarding the fundamentals of cleaning and disinfection.

一个耐用的污染控制系统始于控制污染进入分级区域开始。这个系统分段为从外部环境进入系统前需要的清洗、消毒和灭菌项目。如果没有一个系统来控制污染进入就如同缺失对环境条件的控制。清洗用于控制系统中堵住所有污染物进入的补充是极其困难的。非研磨型活动的清洗以及后续的脏的泥土、液体、微粒和微生物的消散使特定表面的泥土/残留物和生物负荷更低使得消毒更加简单和更加成功的工艺。区域的消毒使用了验证的试剂来对控制和清洗工艺中所发生的误差进行纠正。分级区域的清洗和消毒不是一种预防方法而是一种纠正程序来补偿控制系统的失败。本技术报告中明确的许多相关细节共同帮助提供已被测量具有稳定的可接受的环境条件的成功机会。稳定的控制是最终目的。本技术报告并不旨在代替任何已有的要求或标准，它是一个关于清洗和消毒基本原则的最佳实务参考文件。

17.0 Appendix I: History Of Disinfection

附录 I：消毒的历史

A disinfectant is a substance that kills microorganisms, also known as bacteria, viruses, and other pathogenic microorganisms, on inanimate objects. People were routinely killing microorganisms long before they even knew of their existence. The ancient Egyptians, Persians, and Chinese used whatever substances had been observed to be effective at keeping "pestilence" at bay. Their random observations of the ability of certain substances to prevent food from spoiling, or people from getting sick, led to the discovery of what can be considered the first disinfectants. These early disinfectants included wine, pine pitch, copper, silver, and even mercury. All of these early disinfectants were, of course, poisonous to humans as well at higher concentrations, but they proved useful at lower dosages for preventing rotting and spoilage. Centuries passed before they were purified and the exact mechanisms of their actions (the killing off of the microorganisms that can cause disease) were finally understood.

消毒剂是一种杀灭无生命体上的微生物（又叫：细菌、病毒和其它致病微生物）的一种物质。在知道微生物存在很久之前人们已常规地在杀死它们了。古埃及人、波斯人和中国人使用已被观察有效的不管何种物质来保持瘟疫远离人类。他们随机的观察某特定物质阻止食物变质、或使人们远离疾病的能力，从而发现了那些可以被认为是第一个消毒剂的物质。这些早期消毒剂包括酒、松焦油沥青、铜、银乃至汞。当然，所有这些早期的消毒剂在较高浓度时对人类也是有毒的，但它们证明在低剂量下时防止腐败和变质是有效的。在这些消毒剂被纯化以及它们作用（杀灭可致病的微生物）的确切机理被最终了解前已过去数个世纪。

17.1 Disinfecting Technologies of the Past 过去的消毒技术

The earliest intentional use of a specific chemical, sulfur dioxide, as a disinfectant was reported as far back as 800 BC by the Greek poet Homer. Fumigation and disinfecting vapors were used in AD 500 by Hindu physician Sushruta Samhita. Venetian cargo ships were reportedly fumigated in attempts to control diseases. During the plagues of the Middle Ages, sulfur dioxide was again used to disinfect contaminated items or areas, although fire was also often used in response to this extreme threat.

最早有意使用特殊化学品二氧化硫作为消毒剂的报道要追溯到公元前800年希腊诗人荷马。公元500年印度医师妙闻使用烟熏和消毒蒸汽。威尼斯货般被报道采用烟熏来试图控制疾病。在中世纪的鼠疫期，二氧化硫又一次被用于消毒受污染的物品或区域，同样的火也被常用于对付这个极度的威胁。

When Anton van Leeuwenhoek perfected his microscope in the mid-1600s, he became the first person to view bacteria. A "fellow of insatiable curiosity," Leeuwenhoek also discovered that pepper, vinegar, and other common chemicals killed what he dubbed the "animalcules" (little animals) that he saw with his microscope. Thus, he became the first person to disinfect, or knowingly kill bacteria, with a chemical substance.

当安东 范 列文虎克在17世纪中期完善了他的显微镜，他成为第一个观察细菌的人，这个“贪得无厌好奇心的家伙”列文虎克还用他的显微镜发现胡椒、醋和其它常见化学品杀死那些他看到的“微生物”（小动物），这样，他成为用化学物质消毒或有意识地杀灭细菌的第一人。

Around the same time, Sir Francis Bacon was experimenting with different substances or methods for preventing putrefaction, which he likened to gangrene and other medical conditions. Bacon noted that the process could be prevented by astringents, acids, salt, sugar, or lack of oxygen.

差不多同时，弗兰西斯 培根爵士正在用不同的物质或方法做试验来防止腐败，他把这比作坏疽和其它医疗

条件，培根注意到这个过程可以被收敛剂、酸、盐、糖或缺氧来阻止。

17.2 Disinfecting Technologies in the Age of Chemistry 化学年代的消毒技术

The science of sterilization via chemical methods (that is, using disinfectants) progressed with Sir John Pringle's experiments with various septic and antiseptic solutions in the mid-1700s. His work led to recommendations for using salts, astringents, vegetable gums, and fermented liquors to prevent spoilage and disease. Using salt as the standard, in 1750 he developed a table of coefficients to help compare the effects of these substances to each other and was possibly the first to ever call these chemicals "antiseptics."

在17世纪中期约翰 普林格尔爵士使用各种腐烂物和防腐剂解决方案的试验中使化学方法（即：使用消毒剂）的灭菌科学取得了进展。他的工作引发了推荐使用盐类、收敛剂、树胶和酿造酒类来防止腐败和疾病。使用盐作为标准，在1750年他开发了一个系数表来帮助比较这些物质各自的效力，他大概也是称这些化学品为“防腐剂”的第一人。

Another chemical disinfecting agent, chlorine, was discovered around the same time by Carl Wilhelm Scheele to prevent putrefaction and accompanying noxious odors. This led to the use of calcium hypochlorite in hospitals, sewers, stables, and other areas. Chlorine was used mostly as a deodorant until its germicidal properties were discovered. During World War I, a 0.5% sodium hypochlorite and alkali solution was used to disinfect wounds. Widespread use of chloride salts continues today, especially in the treatment of water.

另一个化学消毒剂氯在同一时期由卡尔 威廉 舍勒发现用于防止腐败以及伴随的有害气味。这导致次氯酸钙在医院、排水沟、马厩和其它区域的使用。在它的杀菌特性被发现之前氯主要用作除臭剂。在第1次世界大战中，0.5%次氯酸钠和碱溶液用于消毒伤口，氯盐的广泛使用持续至今天，特别是在水处理方面。

Creosote, a mixture of phenols distilled from the tar of beech trees, was discovered by Carl (Karl) Ludwig von Reichenbach in 1832 and also was used first as a deodorant to remove noxious odors. The word creosote is derived from two Greek words that mean "I preserve flesh," and it was used widely in medicine to prevent wounds from becoming infected. Later, a mixture of alkylphenols distilled from coal tar creosote was found to be a more effective wound disinfectant. This distillate was emulsified with soap and marketed as Lysol.

杂酚油是一种从山毛榉树的焦油中蒸馏出的酚类混合物，由卡尔 路德维希 冯 瑞生于1832年发现并首次用作除臭剂来去除有害气味。“杂酚油”这个单词是由两个希腊文字得来，意思是“我保存肉”，它被广泛用于医药来防止伤口感染，后来，从炭焦油杂酚油中蒸馏的烷基酚类被发现对伤口消毒更加有效，这种蒸馏物用肥皂乳化以“来苏尔”的名称上市。

Tincture of iodine was introduced to the United States Pharmacopeia (USP) in 1830 and was used to treat wounds during the Civil War. Other chemists began to discover and isolate many more disinfectants, including copper sulfate, sodium permanganate, and various alcohols, sulfurs, acids, and alkalis. In fact, most of today's most common disinfectants have been used since the nineteenth century.

碘酒于1830年被收载于美国药典（USP），在南北战争期间用于处理伤口。其它化学家开始发现并分离了更多的消毒剂，包括硫酸铜、高锰酸钠和各种醇类、硫磺、酸类和碱类。实际上，现在最常用的消毒剂多数是从19世纪开始使用了。

17.3 Discovering Microorganisms as a Basis of Disease 发现微生物是疾病的基础

Theodor Schwan, who was a codiscoverer of yeast cells, used sterile media and heat to demonstrate that microorganisms in the air produce putrefaction. His experiments were later confirmed and expanded upon by Louis Pasteur. Pasteur was a genius who played a major role in the development of the field of microbiology, as well as in advances in chemistry, medicine, and bacteriology. He was one of the first to advocate the use of heat in medical settings to destroy the microorganisms that cause disease but are invisible to the naked eye. After reading Pasteur's

idea that microbes in the air caused putrefaction, Joseph Lister began to experiment with various antiseptics to kill the microorganisms causing wound infection. He found that a phenol called carbolic acid effectively prevented infection of open wounds in his patients. Phenol proved to be a potent germicide that can even kill spores, but it was toxic to the body tissue at full strength. One of his talks in the United States inspired a physician from Missouri named Joseph Lawrence to develop Listerine in 1879, thus immortalizing Lister's name.

酵母细胞的共同发现人泰奥多尔 施旺使用无菌介质并加热证实空气中的微生物产生腐败作用。他的经验后来被路易 巴斯德证实并详细叙述。巴斯德是一个天才，他在微生物学领域的发展中，以及化学、药物学和细菌学方面的进步中扮演着重要角色。他是最早倡导在医疗设施中使用加热来破坏那些肉眼看不见的可致病的微生物的科学家之一。在阅读了巴斯德关于空气中的微生物导致腐败的想法后，约瑟夫 李斯特开始用各种防腐剂做试验来杀灭导致伤口感染的微生物，他发现一种名叫石炭酸的苯酚可有效的防止病人的开创性伤口的感染。苯酚被证明是一种潜在的杀菌剂甚至可杀死孢子，但它在未稀释的情况下对人体组织有毒。一位来自密苏里名叫约瑟夫 劳伦斯的医师受到李斯特在美国的一次讲话的启发，在1879年开发了李施德林®，这样使李斯特的名字永垂不休。

A pharmacist from New York named Robert Johnson was also inspired by Lister's talk, selecting phenols for use on wound dressings as the first product of his surgical products company Johnson & Johnson. Later, the search for other effective phenols would lead to the development of Lysol from coal tar.

一位来自纽约的名叫罗伯特 约翰逊的药剂师同样也受到李斯特讲话的启发，选择苯酚用于伤口绷带作为他外科产品公司强生的第一个产品，在后来寻找其它有效的苯酚类物质时将引发了对源自炭焦油的来苏尔的开发。

Robert Koch later conclusively demonstrated that bacteria cause disease in live tissues and wrote the report "On Disinfection" in 1881 *(16)*. This report compared the ability of various chemical agents to kill bacteria and their spores. Kronig and Paul later expanded on this, noting that bacteria are killed at a faster rate with increasing temperature and/or chemical concentrations. Rideal and Walker later developed the very practical "phenol coefficient method of testing disinfections," modifications of which are still used today *(17)*.

罗伯特 科赫后来总结性证实细菌导致活体组织的疾病并在1881年撰写了“在消毒”的报告*(16)*。该报告比较了不同化学试剂杀灭细菌及其孢子的能力，克罗尼克和保罗后来对其进行了详细描述，指出在增加温度和/或化学试剂浓度时杀灭细菌的速率更快。里迪尔和沃克后来开发了非常实用的“检测消毒的苯酚系数法”，该方法的修订版至今仍在使用*(17)*。

In 1776, Spallanzani found that microorganisms could be destroyed by heat. Some microbes proved to be more resistant and required boiling for about an hour for a surface to be totally sterile (free of microbes). Appert later used this method of heating with boiling water to preserve food during canning. Koch later defined hot air and steam as sterilizing agents. Tyndallization, a process of sterilizing through discontinuous heat, was then developed by John Tyndall to reduce the activity of any sporulation bacteria left after boiling. Louis Pasteur discovered the benefits of using superheated steam in sterilization that killed bacteria as well as spores, which eventually led to the development of the modern autoclave in the mid-1800s.

1776年，斯帕兰扎尼发现微生物可以通过加热破坏，某些微生物证明有更高的抵抗力，需要煮沸约一个小时使表面完全无菌（无微生物）。阿佩尔后来在罐装食品中使用这种沸水加热方法来保存食品，科赫后来明确热空气和蒸汽是灭菌剂。间隙灭菌法，一种通过不连续加热的灭菌工艺，由约翰·丁达尔开发出来用于减少在加热后残留的孢子细菌的活性。路易 巴斯德发现使用过热蒸汽在灭菌时不但可杀死细菌而且也可杀死孢子的益处，这最终引起了在19世纪中叶现代高压灭菌器的开发。

17.4 Microbiological Contamination Control Today 微生物污染控制的今天

Sterilization is the process of totally destroying all microbes using either physical or chemical methods. Once all microorganisms are destroyed, the resulting product or environment is said to be "sterile," or germ-free.

灭菌是使用物理或化学方法完全杀死所有微生物的工艺，一旦所有微生物被破坏，作为结果的产品或环境就是“无菌的”，或没有菌。

Physical methods of sterilization include the processes of dry heat and steam sterilization that were refined in the late 1800s through the work of William Henry along with Pasteur, Koch, and Wolffhugel *(18).* Much later, gas vapors such as ethylene oxide, formaldehyde vapor, and plasma gas were used, although subsequent research proved some of these gases to be too toxic or, in the case of formaldehyde, even carcinogenic. Steam and dry heat sterilization continues to be the method of choice in many settings, including biopharmaceutical and medical device manufacturing. Decontamination of isolators uses a chemical decontamination agent, for example, hydrogen peroxide.

后来在19世纪末，通过威廉 亨利及巴斯德、科赫和Wolffhugel的研究，将灭菌的物理方法精确描述为包括干热和蒸汽灭菌工艺*(18)*。很久以后，气体蒸汽如环氧乙烷、甲醛蒸汽以及等离子气体的使用，虽然后来研究证明部分这类气体毒性太大，比如甲醛甚至有致癌性。蒸汽和干热灭菌仍旧是许多情况下选择的方法，包括生物制药和医疗器械生产。去污染的隔离器使用化学去污染剂，比如：过氧化氢。

Filtration had been used to purify water for centuries before air was filtered through cotton by Schroder and von Dusch in 1854. Devaine then demonstrated that bacteria in the air could be retained in porcelain filters, but it was John Tyndall, in 1877, who clearly demonstrated that a decrease in visible air particulates with their accompanying microorganisms helped maintain sterility in liquids open to this filtered air. Later, the Pasteur-Chamberland filter was devised to filter out bacteria in fluids as well *(19).*

施罗德和冯 杜施在1854年采用棉花过滤空气之前采用过滤来纯化水已达数个世纪。Devaine后来证实空气中的细菌可以被陶瓷滤器截留，但是直到1877年约翰 丁达尔明确证实减少可见的空气微粒及其伴随的微生物有助于暴露于过滤空气中的液体保持无菌。后来，巴斯德-尚柏朗过滤器被设计出用于过滤液体中的细菌*(19)*。

Ultraviolet (UV) radiation was also found to be an effective method of sterilization, first by Rieder in 1898 and then by Gates in 1928. However, the need for direct exposure and the chance that some microbes can "hide" in cracks and crevices have been major limitations of this method. Still, UV radiation is used today for certain situations, assuming procedures are such that all critical surfaces receive maximum exposure for the time needed to kill all of the microorganisms present.

紫外光照射也被发现是一种有效的灭菌方法，首先由里德于1898年发现，后盖茨于1928年也发现了。然而，这个方法的主要局限性是需要直接照射且某些微生物有机会躲在裂缝或缝隙中。在今天紫外照射仍然在某些特定情况下使用，比如规程可以使所有关键表面接受最大暴露并维持杀死所有存在的微生物所要的时间。

The advancement of organic chemistry in the twentieth century brought a wide variety of disinfectants. Although many common disinfectants have been used for centuries, we now have a much better understanding not only of their mechanism of action but also of the possible harm that these chemicals can cause to humans. In addition, because we can now easily grow and isolate microbes, we are better able to test specific disinfectants and antiseptics to help determine the appropriate level of use for all of the various types. Therefore, disinfection research of today is focused mostly on finding a balance between the two variables of effectiveness and safety. The goal is to design procedures that allow for the application of enough disinfectant to effectively remove all of the microbes, but minimize the risk of harm to the product, the workers who have to use these chemicals in their workplace, and the health of the public at large.

20世纪有机化学的进步带来了多种消毒剂的开发，许多常用的消毒剂虽然已使用数个世纪，现在我们不仅更加了解它们的作用机理而且对这些化学品对人类造成的可能危害也更加的了解，而且，因为我们现在可以很容易培养和分离微生物，我们可更好地检测所有不同类型的特定消毒剂和防腐剂来帮助确定适合的浓度水平，因此，今天的消毒研究更多的集中于发现效应和风险两个变量的平衡。目标是设计程序允许使用足够量的消毒剂有效地去除所有的微生物，但是在最大程度上将其对产品，在工作场所必须使用这些化学品的工人以及对公众健康的危害风险降到最低。

18.0 Appendix II: Registration Of Sanitizers, Disinfectants And Sporicides 附录 II：防腐剂、消毒剂和杀孢子剂的注册

Understanding what legislative body is in charge of registrations of sanitizers, disinfectants, and sporicides throughout the world is imperative to understanding their regulation. At the same time, understanding the variable worldwide types of antimicrobial effectiveness claims and test methods for products that will be used for hard-surface disinfection is critically important. In each country the legislative authority is different. In the United States, the Environmental Protection Agency (EPA) governs hard-surface disinfection and related claims. In the European Union (EU), the EU Biocide Regulation as determined and written by the member states replaces the past segregated individual country governing bodies as the new all-encompassing EU legislature. Many who follow Good Manufacturing Practices (GMPs) assume that the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) must approve sanitizers, disinfectants, and sporicides for use in pharmaceutical, biotechnology, and health-care settings. This assumption would be incorrect, as most medicinal governmental registration authorities become involved only if the chemical agent comes in contact with the human body, comes in contact with a medical device that is implanted or inserted into the human body, or is taken internally into the human body.

了解世界范围内负责防腐剂、消毒剂和杀孢子剂注册的立法机构对于了解它们是如何管理来说是必要的。同样的，了解世界范围各种类型使用于硬表面消毒的产品的抑菌效力要求和检测方法是非常重要的。每个国家的立法当局是不同的，在美国，环境保护署（EPA）管理硬表面消毒及相关要求。在欧盟（EU），由成员国表决和起草的EU农药管理法取代了过去的分离的单个国家主管部门而成为新的包罗万象的欧盟立法机构。假如FDA或EMA必须批准防腐剂、消毒剂和杀孢子剂用于制药、生物技术和健康产品设施，那么许多产品要遵守GMP，这种假设是不正确的，因为仅在化学试剂直接接触人体或与埋植于人体的医疗设备接触时，或者是进人体内部时多数医疗管理注册机构才会参与到管理。

As an example, the U.S. FDA registers products (under a 510K registration) that will be used to clean or sterilize medical device products that will come in contact with the human body. This does not include products that will be used for hard-surface disinfection within a controlled environment. Nor does it include pharmaceutical or biotechnology product-contact surfaces where products may be used. Understanding registration authorities and registration claims is imperative in understanding the claims made on products. In the following sections, the U.S. EPA and the EU Biocide Regulation requirements and framework are discussed. These are examples of the types of registration that are required within their legislative regions. In other regions of the world, legislative authorities, antimicrobial effectiveness claims, and associated requirements vary per region. This complex, worldwide multiregistration system is without harmonization and confuses the average end user, who should confer with local, state, and country requirements prior to use of chemical agents for disinfection purposes.

例如，FDA注册那些将用于直接接触人体的医疗设备清洗或消毒的产品（属于510K注册管理），这不包括在受控环境下用于硬表面消毒的产品，也不包括用于制药或生物技术产品接触表面使用的产品。了解注册机构和注册要求对于了解产品相关要求是必要的。在下列章节中讨论了美国EPA和EU农药管理法要求和框架，还有在他们的法律框架内需要注册的类型的举例。在世界的其它区域，立法机构，抑菌效应要求以及相关要求根据所在区域不同而有所不同。这种复杂的，世界各地多次注册体系没有协调机制并且会使终端用户迷糊，当他们使用某化学试剂作为消毒用时应事先与当地的、州和国家的要求进行协商。

19.0 Appendix III: Overview Of The U.S. Environmental Protection Agency 附录：美国 EPA 综述

The United States Environmental Protection Agency (EPA) regulates antimicrobial products under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). FIFRA requires U.S. EPA registration of a pesticide for sale into the U.S. interstate commerce. Every U.S. state, Puerto Rico, and the District of Columbia require registration of FIFRA pesticides, accompanied by a registration fee, to allow the product to be sold or used in their locale. For most states, registration is an administrative function with the state working cooperatively with the EPA. The California Department of Pesticide Regulation of the California Environmental Protection Agency (Cal-EPA) requires submission and approval of supporting data along the same lines as the U.S. EPA. There are occasions where Cal-EPA and the U.S. EPA do not arrive at the same conclusions.

美国EPA根据联邦农药、杀真菌剂和灭鼠剂法案（FIFRA）管理抗微生物产品。FIFRA要求美国EPA对进入州际贸易的农药进行注册，美国每个州、波多黎各自由州以及哥伦比亚特区要求FIFRA农药的注册并收取注册费以允许产品在其区域内销售或使用，对于多数州，注册是州府与EPA合作的管理功能。加州环境保护署（Cal-EPA）的加州农药监管部门与美国EPA以同样的方式来要求提交和批准支持性数据，Cal-EPA和美国EPA偶尔也会得出不同的结论。

The U.S. EPA's authority is based on the FIFRA definitions of *pesticide* and *pest.* According to FIFRA, Section 2 (u), a pesticide is "any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest, any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant and any nitrogen stabilizer" *(20).* According to FIFRA Section 25 (c) (1), a pest is "any insect, rodent, nematode, fungus, weed or any other form of terrestrial or aquatic plant or animal life or virus, bacteria or other micro-organism (except viruses, bacteria or other micro-organisms on or in living man or other living animals) which the Agency declares to be a pest" *(20).* Antimicrobial agents are substances used to destroy or suppress the growth of harmful microorganisms, whether bacteria, viruses, or fungi, on inanimate objects and surfaces.

美国EPA的权力是基于FIFRA所定义的农药和害虫。根据FIFRA章节2 (u)，农药是“用于预防、消灭、驱赶或减轻任何害虫的物质或混合物质”，“用作植物调节剂、落叶剂或干燥剂和任何的氮稳定剂的物质或混合物质” *(20)*。根据FIFRA 章节25 (c) (1)，害虫是“任何管理当局公告为害虫的昆虫、啮齿动物、线虫、真菌、杂草或任何陆生或水生植物的其他形式，或动物生命或病毒、细菌或其他微生物（除了活的人体或其他活的动物体内或表面的病毒、细菌或其它微生物以外）” *(20)*。抗微生物试剂是用于消灭或抑制无生命体或表面上的细菌、病毒或真菌类有害微生物的物质。

Registrants of antimicrobial products must demonstrate that the product will not cause unreasonable adverse effects to human health or the environment. Data must be submitted or cited in support of registration, including detailed information on the chemical composition of the product, the chemical characteristics of the formulation, effectiveness data to support their claims against specific microorganisms, and toxicity data. Much of the labeling verbiage is prescriptive and based on the chemistry, safety, and efficacy data.

抗微生物产品的注册必须证实产品不会对人体健康或环境产生不合理的不良反应，必须提交或引用数据来支持注册，包括产品化学组分、制剂的化学特性、支持它们针对特定微生物所要求的效力数据和毒理数据的详细信息。多数的标签用词是规范的且基于化学、安全性和有效性数据。

The EPA recognizes efficacy claims as either public health claims or non-public-health claims. Public health claims

are for the control of microorganisms infectious to humans in or on any inanimate environment. Non-public-health claims are for the control and growth of algae; odor-causing bacteria; bacteria that cause spoilage, deterioration, or fouling of materials; and microorganisms infectious only to animals. This general category includes products used in cooling towers, paints, and treatments for textile and paper products. Standard efficacy methods are established to be used to generate data in support of registration.

EPA将功效要求分为公众健康要求或非公众健康要求，公众健康要求是对在任何无生命体环境内或上对人类感染微生物的控制。非公众健康要求是对材料中藻类、产生异味的细菌、导致腐败的细菌、变质或污染以及仅对动物的微生物感染的控制和增长，这个一般类别包括用于冷却塔、涂料、纺织品和纸制品的处理的产品。应建立标准的功效方法来用于生成数据以支持注册。

Registration decisions are made by the EPA on a "risk vs. benefit" approach. Antimicrobials are biocides and often present risk to nontarget organisms, including humans. The EPA examines the safety of the product by assessing worker safety, food safety (when applicable), effects on nontarget organisms, and effects on surfaces by reviewing acute and chronic safety studies and exposure risk assessments of both active ingredients and the finished product. The EPA establishes procedures through product labeling to reduce the inherent risk associated with the use of these biocides.

EPA根据风险-收益方法来做出注册决定，抗微生物试剂是杀菌剂通常对非靶标生物体包括人类也存在风险，EPA通过评价劳动者安全性、食品安全性（必要时）来检查产品的安全性，对非靶标生物体的效力以及通过审核急性和慢性安全性数据检查对表面的效力以及活性成分和成品的暴露风险评估来检查产品的安全性。EPA通过产品标签建立程序来减少这些杀生物剂使用相关的内在风险。

To assess the efficacy of antimicrobials, the EPA requires manufacturers of these chemical agents to perform specific testing. See Appendix VI for AOAC protocol testing for disinfectant registration.

为了评价抗微生物试剂的效力，EPA要求这些化学试剂的生产商进行特定检测，见附录VI：消毒剂注册的AOAC协议测试。

Although the EPA regulates efficacy data for sanitizers, disinfectants, and sporicides, pharmaceutical, biotech, and medical device manufacturers are not alleviated from FDA and EMA disinfectant validation requirements. Therefore, pharmaceutical, biotech, and medical device companies are required to show performance data against their site-specific isolates as part of their disinfectant validation process. CFR Title 40 registration information is located at http://www.epa.gov *(21)*.

虽然EPA管理防腐剂、消毒剂和杀孢子剂的效力数据，制药、生物技术和医疗器械生产商不能减轻FDA和EMA的消毒剂验证要求，因此，制药、生物技术和医疗器械公司被要求展示作为他们消毒剂验证工艺一部分的针对其特定场所隔离种群的性能数据。CFR标题40注册信息见http://www.epa.gov *(21)*。

20.0 Appendix IV: Overview Of The EU Biocidal Regulations

附录 IV：欧盟农药管理法综述

The introduction of the Biocidal Products Regulation 98/8/EC (BPR) brought into enforcement the requirement to gain approval (via registration) to supply biocide products of all types to the EU market. This includes clean room disinfectants. The BPR replaces individual country registration systems for active ingredients.

生物杀灭剂法规98/8/EC（BPR）的引入并进入实施，要求获得批准（通过注册）以供应所有类型的杀生物剂产品至欧盟市场，这包括洁净室消毒，BPR替代了活性成分在单个国家的注册系统。

The BPR takes into consideration new and existing active substances. New active substances can no longer be placed on the market in the EU until full approval is granted—this applies now.

BPR将新的和已有的活性成分包含在内，新活性成分在获得充分批准前不能投放在欧盟市场---这适用于现在。

In the case of existing active substances, the European Commission introduced a transitional period to allow suppliers to develop the necessary data for submission to, and evaluation by, the authorities in order to gain approval to supply.

对于已有的活性成分，欧洲委员会引入了过渡期来允许供应商开发必要的数据用于递交供管理当局评价以获得批准来供应市场。

During this transitional period, individual countries can continue with their national approval systems until active substances used in disinfectants are called in for evaluation under the BPR. At this time all national approvals schemes will be phased out. Those that successfully negotiated the evaluation process gained what is known as an Annex 1 to BPR listing, allowing them to be used in formulated products throughout the EU without the need for individual national approvals, as was previously the case.

在过渡期期间，单个国家可以继续使用其国家批准系统直到消毒剂中所用的活性成分按照BPR被要求进行评价为止，在这个时候所有的国家批准方案将被淘汰，那些成功免除评价过程也就是BPR列表的附件1中的产品不需要单个国家的批准在欧盟范围内使用于制剂产品中，就像原来一样。

A competent authority in any EU member country can approve a formulated product containing an active substance listed in Annex 1. Once a formulated product has been authorized in one member country, it will be possible for it to be mutually recognized and approved for sale in other member countries, although there may be some specific local requirements that must be met. An application must be made to each member country in which the formulated product will be sold, and fees will be payable for these processes. Achieving Annex 1 listing triggers the next phase of registration, which involves the systematic evaluation of all formulated products.

欧盟任何成员国的管理当局可以批准含有附件1列表中活性成分的制剂产品，一旦一个制剂产品在一个成员国获批，它则可能通过互认并批准在其它成员国销售，虽然这可能需要必须符合某些特定的当地要求。制剂产品需要在其国销售的话，每个成员国必须要做一个申请，这些过程将要付费。获得附件1列表引发下一阶段的注册，包括对制剂产品的系统评价。

A major part of the dossier for each formulated product is the efficacy assessment. Although there is no ranking for the efficacy test methods, at the top of the commission wish list are the EN test methods. Over the past few years there has been an aggressive program to develop new EN test methods applicable for use to support biocide product testing. It is expected that as these become available, they will eventually replace current national standards. See

Appendix VII for EN test method information.

每个制剂产品文档的主要部分是功效评定，虽然功效检测方法没有等级，委员会的高层希望是欧洲标准（European Norm，简称EN）检测方法，在过去的数年已有积极的程序来开发新EN检测方法应用于支持杀生物剂产品的检测，所能预料到的是如果有EN方法，将最终代替现有的国家标准，见附录VII：EN检测方法信息。

The new BPR regulations are not industry specific, nor are they very specific to clinical health-care requirements covering hospital ward and theater situations. They have little to do with EU GMP or pharmaceutical production in clean room environments.

新BPR法规不是工业特定的，也不是专门针对覆盖医院病房和手术室的临床卫生保健要求，他们需要做一些欧盟GMP或在洁净区的制药生产有关的一些工作。

The BPR is a major task, which will take time to be brought into full effect. Further details about the BPR can be found at http://ec.europa.eu/environment/biocides/index.htm.

BPR是一个主要任务，它需要时间进入全面生效，BPR的进一步信息可见 http://ec.europa.eu/environment/biocides/index.htm。

21.0 Appendix V: EPA-Related Safety Labeling Information

附录 V：EPA 相关的安全标签信息

Labeling requirements for antimicrobial products vary by country. For those antimicrobial productsregistered in the United States, the EPA provides prescriptive precautionary label verbiage *(22).* Thisverbiage is typically determined by the results of six acute toxicity studies performed with the productformulation. The acute oral, acute dermal, and acute inhalation studies evaluate systemic toxicity viathe designated routes of exposure. The primary eye irritation and primary skin irritation studies measure irritation or corrosion, while the dermal sensitization study evaluates the potential for allergic contact dermatitis. With the exception of dermal sensitization, each acute study is assigned to a toxicitycategory based on the study results (See Table 21.0-1 below). The results of these six acute toxicitystudies must be known in order for the appropriate labeling language to be determined. Table 21.0-2provides the required precautionary language based on the assigned toxicity category.

杀菌剂的标签要求随国家不同而变化。对那些在美国注册的杀菌剂来说，EPA提供了规范的预警标签措辞（22）。这些措辞通常由用产品实施的六个急性毒性研究结果确定。口服急性，皮肤急性和急性吸入研究通过指定途径的暴露对全身毒性进行评价。原发性眼刺激和原发性皮肤刺激研究测量了刺激或腐蚀程度，而皮肤致敏研究评价了过敏性接触性皮炎的可能性。除了皮肤致敏研究之外，根据研究结果（见下表21.0-1）将每个急性研究都归属到一个毒性类别。为了确定正确的标签用语，必须知道这六个急性毒性研究的结果。根据所归的毒性类别，表21.0-1提供了所需的预警用语。

Table 21.0-1 Toxicity Categories *(22)*

表 21.0-1 毒性类别 *(22)*

Study 研究	Category I I类	Category II II类	Category III III类	Category IV IV类
Acute oral	Oral LD50 up to and including 50mg/kg	>50 through 500mg/kg	>500 through 5,000 mg/kg	>5,000 mg/kg
口服急性	口服LD50达到并包括50mg/kg	>50 到 500mg/kg	>500 到5,000 mg/kg	>5,000 mg/kg
Acute dermal	Dermal LD50 up to and including 200mg/kg	>200 through 2,000 mg/kg	>2,000 through 5,000 mg/kg	>5,000 mg/kg
皮肤急性	皮肤LD50达到并包括200mg/kg	>200 到 2,000 mg/kg	>2,000 到 5,000 mg/kg	
Acute inhalation (4-hour exposure)	Inhalation LD50 up to and including 0.05 mg/liter	>0.05 through 0.5 mg/liter	>0.5 through 2 mg/liter	> 2 mg/liter
吸入急性（4小时的暴露）	吸入LD50达到并包括0.05mg/升	>0.05到 0.5 mg/升	>0.5到 2 mg/升	> 2 mg/升
Primary eye irritation	Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days	Corneal involvement or other eye irritation clearing in 8-21 days	Corneal involvement or other eye irritation clearing in 7 days or less	Minimal effects clearing in less than 24 hours

原发性眼刺激	腐蚀（眼组织不可逆损害）或角膜受累或刺激持续21天以上	角膜受累或其它眼刺激在8-21天内消失	角膜受累或其它眼刺激在7天或小于7天内消失	影响极小在低于24小时内消失
Primary skin irritation	Corrosive (tissue destruction into the dermis and/or scarring)	Severe irritation at 72 hours (severe erythema or edema)	Moderate irritation at 72 hours (moderate erythema)	Mild or slight irritation at 72 hours (no irritation or slight erythema)
原发性皮肤刺激	腐蚀（组织损害至真皮和/或瘢痕形成）	72小时严重刺激（严重的红斑或水肿）	72小时中度刺激（中度红斑）	72小时轻度或轻微刺激（无刺激或轻微红斑）

Table 21.0-2 Precautionary Statements by Route Entry

表 21.0-2 按照进入途径分的预警声明

Acute Oral Toxicity 口服急性毒性	
Toxicity category 毒性类别	Statements 声明
I	Fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet.
	吞食后会致命。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。
II	May be fatal if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet.
	如果吞食可能致命。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。
III	Harmful if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet.
	吞食后对人体有害。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。
IV	No statements are required. However, the registrant may choose to use category III labeling.
	不需要声明。但是，注册人可以选择使用III类的标签。
Acute Dermal Toxicity 皮肤急性毒性	
Toxicity category 毒性类别	Statements 声明
I	Fatal if absorbed through skin. Do not get in eyes, on skin, or on clothing. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet. Wear [specify appropriate protective clothing]. Remove and wash contaminated clothing before reuse.
	通过皮肤吸收后会致命。勿使其进入眼睛，沾到皮肤上或衣服上。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。应穿着特定的适当的防护服。脱去受污染的衣服，在再次使用前清洗干净。
II	May be fatal if absorbed through skin. Do not get in eyes, on skin, or on clothing, wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet. Wear [specify appropriate protective clothing]. Remove and wash contaminated clothing before reuse.
	通过皮肤吸收后可能会致命。勿使其进入眼睛，沾到皮肤上或衣服上。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。应穿着特定的适当的防护服。脱去受污染的衣服，在再次使用前清洗干净。
III	Harmful if absorbed through skin. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking ,and chewing gum, using tobacco

	or using the toilet. Remove and wash contaminated clothing before reuse. Wear [specify any appropriate protective clothing, if appropriate].
	通过皮肤吸收后对人体有害。避免与皮肤、眼睛或衣服接触。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。脱去受污染的衣服，在再次使用前清洗干净。适当时，应穿着特定的适当的防护服。
IV	No statements are required. However, the registrant may choose to use category III labeling. 不
	需要声明。但是，注册人可以选择使用III类的标签。
Acute Inhalation Toxicity 吸入急性毒性	
Toxicity category 毒性类别	Statements 声明
I	Fatal if inhaled. Do not breathe (dust, vapor, or spray mist). * Wear [specify appropriate respiratory protection from Table 4, Chapter 10 of EPA Label Review Manual]. Remove and wash contaminated clothing before reuse.
	吸入后会致命。不得吸入（粉尘、蒸汽或喷雾）。*穿戴EPA标签审核手册第十章表4中规定的适当的呼吸防护装置。脱去受污染的衣服，在再次使用前清洗干净。
II	May be fatal if inhaled. Do not breathe (dust, vapor or spray mist).* Wear [specify appropriate respiratory protection from Table 4, Chapter 10 of EPA Label Review Manual]. Remove and wash contaminated clothing before reuse.
	吸入后可能会致命。不得吸入（粉尘、蒸汽或喷雾）。*穿戴EPA标签审核手册第十章表4中规定的适当的呼吸防护装置。脱去受污染的衣服，在再次使用前清洗干净。
III	Harmful if inhaled. Avoid breathing (dust, vapor or spray mist). * remove and wash contaminated clothing before reuse.
	吸入对人体有害。不得吸入（粉尘、蒸汽或喷雾）。*脱去受污染的衣服，在再次使用前清洗干净。
IV	No statements are required. However, the registrant may choose to use category III labeling.
	不需要声明。但是，注册人可以选择使用III类的标签。
* Choose the word which appropriately describes the product during use.	
*在使用中选择恰当的描述用语。	
Primary Eye Irritation 原发性眼刺激	
Toxicity category 毒性类别	Statements 声明
I	Corrosive. * Causes irreversible eye damage. Do not get in eyes or on clothing. Wear [specify appropriate protective eyewear such as goggles, face shield, or safety glasses]. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.
	腐蚀品。*引起不可逆的眼损伤。避免进入眼睛或沾到衣服上。穿戴规定的适当保护镜如护目镜、防护面罩或安全眼镜。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。脱去受污染的衣服，在再次使用前清洗干净。
II	Causes substantial but temporary eye injury. Do not get in eyes or on clothing. Wear [specify appropriate protective eyewear such as goggles, face shield, or safety glasses]. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.
	造成实质性的但是暂时的眼损伤。避免进入眼睛或沾到衣服上。穿戴规定的适当保护镜如护目镜、防护面罩或安全眼镜。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。脱去受污染的衣服，在再次使用前清洗干净。
III	Causes moderate eye irritation. Avoid contact with eyes or clothing. Wear [specify protective eyewear, if appropriate]. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing, gum, using tobacco or using the toilet.
	造成中度眼刺激。避免与眼睛接触或沾到衣服上。穿戴规定的适当保护镜如护目镜、防护面罩或安全眼镜。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗

IV	No statements are required. However, the registrant may choose to use category III labeling.
	不需要声明。但是，注册人可以选择使用III类的标签。
* The term “corrosive” is not required if corrosive effects were not observed during the study.	
*如果在研究中未观察到腐蚀作用，则不需使用“腐蚀品”一词	
Primary Skin Irritation 原发性皮肤刺激	
Toxicity category 毒性类别	Statements 声明
I	Corrosive. Causes skin burns. Do not get in eyes, on skin, or on clothing., wear [specify appropriate protective clothing and gloves]. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.
	腐蚀品。造成皮肤灼伤。避免进入眼睛、沾到皮肤或衣服上。穿戴规定的适当防护服和手套。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。脱去受污染的衣服，在再次使用前清洗干净。
II	Causes skin irritation. Do not get on skin or on clothing. Wear [specify appropriate protective clothing and gloves]. Wash thoroughly with soap and water after handling and before eating, drinking, and chewing gum, using tobacco or using the toilet. Remove and wash contaminated clothing before reuse.
	造成皮肤刺激。避免进入沾到皮肤或衣服上。穿戴规定的适当防护服和手套。使用后，进食、饮水、吃口香糖、吸烟和如厕之前用肥皂和水彻底清洗。脱去受污染的衣服，在再次使用前清洗干净。
III	Avoid contact with skin or clothing, wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear [specify protective clothing and gloves, if appropriate].
	避免接触皮肤或衣服，使用后，进食、饮水、吃口香糖或吸烟之前用肥皂和水彻底清洗。如适用，穿戴规定的适当的防护服和手套。
IV	No statements are required. However, the registrant may choose to use category III labeling.
	不需要声明。但是，注册人可以选择使用III类的标签。

Dermal Sensitization 皮肤致敏	
Study result 研究结果	Statement 声明
Product is a sensitizer or is positive for sensitization	Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.
本品为一种致敏剂或致敏作用阳性。	长时间或频繁接触皮肤会导致一些人的过敏反应。
Product is not a sensitizer or is negative for sensitization	No labeling is required for thisresult.
本品不是致敏剂或致敏作用阴性。	这样的结果不需要标明。

22.0 Appendix VI: AOAC Protocol Testing

附录 VI： AOAC方案测试

For Disinfectant Registration

用于消毒剂注册

Firms registering antimicrobial products are required by the U.S. EPA or other international authorityto submit or cite, in support of registration, detailed information on the formula of the product, thechemical or physical characteristics of the formulation, effectiveness data to support claims againstspecific microorganisms, and safety or toxicity data. While this type of testing is required by the U.S.EPA for manufacturers of marketed antimicrobial products, it should not be considered a mandatory requirement for GMP operations. Furthermore, GMP operations do not utilize an AOAC protocol for their antimicrobial effectiveness; however, the U.S. EPA approval should be verified by the user during the selection process of an appropriate disinfection agent. See http://www.eoma.aoac.org forspecific AOAC methods *(23)*.

美国EPA或其它国际权威机构要求注册抗菌剂的公司提交或引用详细的产品配方信息、制剂的理化性质、支持其声明的针对特定微生物的有效性资料和安全性或毒性资料，为注册提供支持。尽管美国EPA要求已上市抗菌剂的生产商提供这种类型的试验，但这不被认为是GMP操作的强制性要求。此外，GMP操作并不使用AOAC方案来测试其抗菌有效性。然而，应当通过用户在选择合适的消毒剂的过程中对美国EPA的批准进行证实。特定的AOAC方法见http://www.eoma.aoac.org *(23)*。

Performance claims require the generation of efficacy data under controlled testing conditions. Data generated in support of claims for microorganisms that are pathogenic to humans must be submittedto the EPA for review and approval. Data generated for microorganisms not considered pathogenic to humans under certain conditions do not always need to be submitted to the agency but must be on file and available to the EPA upon request.

性能声明要求在受控的检测条件下生成有效性数据。所生成的用于支持对人致病微生物声明的数据必须提交到EPA进行审评和批准。在特定条件下对人体不致病的微生物产生的数据并不要求全部提交给当局，但必须存档，在EPA索取时需要提供。

Generation of data to support label claims and product registration may be conducted under the following approaches:

用于支持标签声明和产品注册的数据可通过以下途径生成：

- Recognized consensus methods
- 公认的共识的方法
- EPA-approved protocols
- EPA批准的方案
- Published peer-reviewed data (rarely used)
- 已发布的同行评议资料（很少使用）

Test data are generated against specific microorganisms or surrogate organisms identified by the EPA as acceptable

marker organisms. The EPA has recognized or established standard methodology and continues to work cooperatively with interested parties to develop improved consensus methods.

针对特定微生物或EPA认定为可接受的标记生物的替代生物生成试验数据。EPA已经认可或建立了标准化的方法学并与有关各方持续合作开发改良的共识方法。

The general efficacy label claims (indications) recognized by the EPA are as follows:

EPA认可的通用有效性标签声明（适用范围）如下：

- Sporicides (also termed "cold sterilants") are used on hard inanimate surfaces and objects toeliminate all forms of microbial life, including fungi, viruses, and all forms of bacteria and spores.
- 杀孢子剂（也称为“冷灭菌剂”）用于坚硬的无生命的表面和物体以消灭所有形式的微生物，包括霉菌、病毒和各种细菌和孢子。

Spores are considered the most difficult form of microorganism to destroy. Therefore, the EPA and other chemical registration organizations consider the term *sporicide* to be synonymous with cold sterilant

孢子被认为是最难破坏的微生物。因此，EPA和其它化学注册机构将*杀孢子剂*一词作为冷灭菌剂的同义词。

- Disinfectants are used on hard inanimate surfaces and objects to eliminate or irreversibly inactivate infectious bacteria but not necessarily their spores. The EPA treats the terms *germicide* and *bactericide* as synonymous with *disinfectant.* Disinfectant products are divided into two major categories:
- 杀孢子剂用于坚硬的无生命表面和物体以消灭或不可逆地灭活感染性细菌但不一定是其孢子。EPA将*杀病菌剂*与*杀细菌剂*作为*消毒剂*的同义词。消毒剂产品被分为两个主要的类别：

1. Hospital Use: Hospital-type disinfectants are the most critical to infection control and are used in health-care settings.
   医院用：医院类型的消毒剂是对于控制感染最为关键的，并且用于卫生保健设施。
2. General Use: General disinfectants are the major source of products used in households, swimming pools, and water purifiers.
   一般用途：一般消毒剂主要用于家庭，游泳池和净水器。

- Fungicides are agents used to reduce, but not necessarily eliminate, microorganisms from the inanimate surfaces to levels considered safe as determined by public health codes or regulations.
- 杀真菌剂用来减少但不必须消灭无生命表面的微生物至公共卫生法规确定为安全的水平。

Sanitizers include food-contact and non-food-contact surfaces.

消毒剂包括食品接触和非食品接触表面用。

- Tuberculocides are agents that destroy or irreversibly inactivate tubercle bacilli in the inanimate environment.
- 杀结核菌剂破坏或不可逆地灭活无生命环境中的结核杆菌。
- Virucides are agents that destroy or irreversibly inactivates viruses in the inanimate environment
- 杀病毒剂破坏或不可逆地灭活无生命环境中的病毒。

The U.S. EPA test requirements for registering label claims or indications are summarized below.

美国EPA注册标签声明或适用范围的试验要求总结如下：

Depending on the country and registration requirements, other tests and acceptance criteria may be required.

根据不同的国家和注册要求，可能需要其它的试验和可接受标准。

- Sterilizer claim requirements: AOAC Sporicidal Test [60 Carriers each on two surfaces (porcelain penicylinders and silk suture loops)] against spores of *Bacillus subtilis*(ATCC 19659) and *Clostridium sporogenes*(ATCC 3584) [three samples representing three lots, one lot 60 days old, killing all 720carriers]. One lot tested independently is required by the U.S. EPA.
- 杀菌器的声明要求：针对枯草牙孢杆菌（ATCC19659）孢子【两个表面，每个表面上60个载体（瓷制小管和丝线圈）】和生孢梭菌（ATCC3584）孢子【代表三批次的三个样品，一批存放60天，杀灭全部720个载体】的AOAC杀孢子试验。美国EPA要求单独做一批检验。
- Disinfectant (limited efficacy) requirements: AOAC Use-Dilution Method or AOAC Germicidal Spray Products Test against *Salmonella choleraesuis*(ATCC 10708) or *Staphylococcus aureus*(ATCC6538) [60 carriers testing three samples representing three different lots, one lot 60 days old killing 59 out of each set of 60 carriers].
- 消毒剂（有限的效力）要求：针对猪霍乱沙门氏菌（ATCC10708）或金黄色葡萄球菌（ATCC6538）的AOAC使用-稀释法或AOAC杀菌喷雾产品试验【60个载体检测代表三个不同批次的三个样品，有一批存放60天，杀灭每组60个载体中的59个】。
- Disinfectant (hospital or medical environment) requirements: AOAC Use-Dilution Method or AOAC Germicidal Spray Products Test against *S. choleraesuis*(ATCC 10708), *S. aureus*(ATCC 6538),and *Pseudomonas aeruginosa*(ATCC 15442) [60 carriers testing three samples representing three different lots, one lot 60 days old killing 59 out of each set of 60 carriers],
- 消毒剂（医院或医学环境）要求：针对猪霍乱沙门氏菌（ATCC10708）或金黄色葡萄球菌（ATCC6538）和铜绿假单孢菌（ATCC15442）的AOAC使用-稀释法或AOAC杀菌喷雾产品试验。【60个载体检测代表三个不同批次的三个样品，一批存放60天，杀灭每组60个载体中的59个】。
- Fungicide requirements: AOAC Fungicidal Test or versions of the AOAC Use-Dilution Method or Germicidal Spray Products Test modified with appropriate elements in the AOAC Fungicidal Test against *Trichophyton mentagrophytes*(ATCC 9533) [10 carriers testing two samples representing twodifferent lots killing all fungal spores],
- 杀霉菌剂要求：针对须毛癣菌（ATCC9533）的AOAC杀霉菌试验或AOAC使用-稀释法的版本或用AOAC钉霉菌试验中的适当要素修订后的杀菌喷雾产品试验【10个载体检测代表两个不同批次的样品，杀灭所有的霉菌孢子】。
- Virucide requirements: Carrier methods as modifications of either the AOAC Use-Dilution Methodor the AOAC Germicidal Spray Products Test against the particular virus with a recoverable virus titer of at least 104 from the test surface [two different lots of four determinations per each dilution showing inactivation of virus at all dilutions when no cytotoxicity is observed and at least a three log reduction in viral titer for both samples when cytotoxicity is present].
- 杀病毒剂要求：针对特定病毒，按照AOAC使用-稀释法或AOAC杀菌喷雾产品试验修订的载体方法，从测试表面上可回收的病毒滴度至少为104【两个不同批号每个稀释水平进行四次测定，在所有稀释水平下显示出能够灭活病毒，而无细胞毒性，并且在出现细胞毒性时两个样品的病毒滴度至少有三个对数级别的降低】。
- Tuberculocide requirements: Tuberculocidal Activity Method or the AOAC Germicidal SprayProducts Test modified to meet the requirements of the Tuberculocidal Activity Method against*Mycobacterium tuberculosis* var. bovis (BCG) [two samples representing two different lots killing the entire test microorganism on all carriers and no growth in any of the inoculated tubes of two additional media]. Alternative

method—Quantitative Tuberculocidal Activity Test (four log kill required). Products with tuberculocidal claims that are formulated with quaternary ammoniumcompounds may be evaluated for tuberculocidal efficacy using any one of the test methods listedabove. However, validation data are required for any test method chosen. Validation data must bedeveloped by testing one additional sample of the product by a laboratory of the registrant's choice(other than the laboratory that developed the original efficacy data) using the *same* optional test procedure and test conditions as the original laboratory.

- 杀结核菌要求：针对结核杆菌bovis种（*Mycobacterium tuberculosis* var. bovis）(BCG)的杀结核菌活性法或经修订符合杀结核菌活性法的APAC杀菌喷雾产品试验【代表两个不同批次的两个样品杀灭所有载体上的全部供试微生物并且另外两个培养基接种管中均无生长】。备用方法-杀结核菌活性定量法（要求四个对数级别的杀灭）。标有杀结核菌作用且配方中含有季铵盐的产品应使用上述任何一种检验方法评价杀结核菌的效力。然而，选用任何一种试验方法都需要进行验证。注册申请人必须选择一个试验室（而不是产生有效性原始数据的试验室），在与原试验室使用*相同*的检验方法和检验条件下检验产品的另一个样品来得到验证数据。

- Non-food-contact sanitizer requirements: Guideline 91-30 Method No. 8 against *Staphylococcusaureus*(ATCC 6538) and either *Klebsiellapneumoniae*(ATCC 4352) or *Enterobacteraerogenes*(ATCC13048) on representative surfaces depending on the proposed uses, including but not limited toglass, metal, unglazed or glazed ceramic tile, or vitreous china showing a bacterial reduction of atleast 99.9% over the parallel control count within five minutes.

- 不得接触食品的消毒剂要求：针对金黄色葡萄球菌（ATCC6538）和肺炎杆菌（ATCC4352）或和产气肠杆菌（ATCC13048）的91-30指南第8法，在有代表性表面上（取决于使用目的），包括但不限于玻璃、金属、未上釉或釉面瓷砖或玻璃瓷，在五分钟内，至少显示出高于平行对照计数99.9%的细菌减少。

- Food-contact sanitizer requirements: For Halide Chemical Products: AOAC Available Chlorine Germicidal Equivalent Concentration Method against *Salmonella typhi*(ATCC 6539) [One test on each of three samples representing three lots, one that is at least 60 days old showing product concentrations equivalent in activity to 50, 100, and 200 ppm of available chlorine]. For otherchemical products, such as quaternary ammonium compounds, chlorinated trisodium phosphate,and anionic detergent-acid formulations: AOAC Germicidal and Detergent Sanitizers Method against *Escherichia coli* (ATCC 11229) and *Staphylococcus aureus*(ATCC 6538) [one sample from eachof three different lots, one of which is at least 60 days old, onstrating 99.999% reduction in thenumber of each test organism within 30 seconds].

- 与食品接触的消毒剂要求：对于卤化物消毒剂产品：针对伤寒杆菌（ATCC6539）的有效氯杀菌等效浓度法【三批代表性样品每个做一次检验，有一批存放至少60天，显示产品浓度在活性上相当于50，100和200ppm的有效氯】。对于其它化学消毒剂产品，如季铵盐化合物、氯化磷酸三钠和阴离子洗涤剂-酸制剂：针对大肠杆菌（ATCC11229）和金黄色葡萄球菌（ATCC6538）的AOAC杀菌和清洁消毒剂法【三个不同批次各取一个样品，其中有一个样品至少存放60天，在30秒内每种试验微生物应在数量上减少99.999%】。

- Additional organism requirements: (applies to specific microorganisms other than those namedby the AOAC Use-Dilution Method, AOAC Germicidal Spray Products Test, AOAC FungicidalTest, and AOAC Tuberculocidal Activity Method and not including viruses): AOAC Use-DilutionMethod or AOAC Germicidal Spray Products Test against the specific organism [10 carriers testingtwo samples representing two different lots killing all carriers].

- 额外的微生物要求：（适用于AOAC使用-稀释法、AOAC杀菌喷雾产品试验、AOAC杀霉菌试验和AOAC杀结核杆菌活性法中未提到的特定微生物，不包括病毒）针对特定微生物的AOAC 使用-稀释法或AOAC

杀菌喷雾产品试验【10个载体检测代表两个不同批次的两个样品，杀灭所有载体】

- Other, more specific claims include residual self-sanitizing activity of dried chemical residue, towelettes, air sanitizers, laundry additives, carpet sanitizers, drinking water, swimming pool water,and preservatives.
- 其它更特定的声明包括干化学残留物、小毛巾、空气消毒剂、洗衣房添加剂、地毯消毒剂、饮用水、游泳池水和防腐剂的残留自消毒活性。
- Other circumstance and variables to consider are confirmatory efficacy testing, organic soil load(one-step application) claim, and hard water claim (400 ppm).
- 要考虑的其它情况和可变因素有确定性效力试验、有机质土壤负荷（一步应用）声明，和硬质水声明（400ppm）。

Alternative methods necessary for special application methods or unique organism testing wherestandard methods are not appropriate require EPA review and approval of protocols prior to generation and submission of the data.

对于特殊应用或唯一生物体检验所需，并且标准方法不适用的备选方法，在数据生成和提交前需要EPA对方案进行审核并批准。

Several end users in the pharmaceutical, biotech, and medical device industries have modified the log reduction requirements for AOAC methods. This has been done to reflect normally lower bioburden levels in controlled manufacturing environments. End users have utilized these methods against their environmental isolates.

制药、生物技术和医疗器械产业的一些终端用户修改了AOAC方法的对数下降要求。这个修改反映了在受控的生产环境中生物负荷水平通常较低。终端用户对他们的环境分离菌使用这些方法。

Additionally, end users will typically look for a log reduction (at a 104 inoculate level) of three logs for vegetative bacteria on hard surfaces and two logs for spore-forming bacteria on hard, nonporous surfaces. The log reduction may vary depending on organisms and conditions tested. Worst-case environmental monitoring data should be the guide for deciding the required effectiveness of the chemical agents.

此外，终端用户通常希望硬质表面上的细菌繁殖体有三个对数级别的减少（在104的接种量水平），在硬质的无孔表面上孢子形成细菌有两个对数级别的减少。对数减少量随着生物体和检测环境的不同而变化。最差条件的环境监测数据应成为决定化学剂所需的效力的指导。

The AOAC methods are normally used for U.S. EPA registration purposes only. Typically, pharmaceuticaland biotechnology operations utilize a carrier surface study or a suspension study or both.

AOAC方法通常仅用于美国EPA注册的目的。尤其是制药和生物技术操作使用载体表面研究或悬液研究或两者都用。

23.0 Appendix VII: EN Tests For Disinfection Efficacy

附录 VII：EN 的消毒效果检验

The acceptance criteria for registration efficacy depend on which EU standard is being met. This is thebasis for the efficacy claims on the product.

注册效果的可接受标准取决于符合哪个EU标准。这是产品效果声明的根据。

Test methods follow a three-phase evaluation:

检验方法遵循三阶段评价：

- Phase 1: Suspension test to determine basic bactericidal, fungicidal, or sporicidal activity The testprotocol gives no specific contact time and does not require interfering substances to be added.
- 阶段1： 悬液检验以确定基本杀菌、杀霉菌或杀孢子活性。检验方案没有提到特定的接触时间，也没有要求添加干扰物质
- Phase 2: Tests for defined applications:
- 阶段2：既定应用的检验
  - Step 1: Suspension test to determine bactericidal, fungicidal, virucidal, or sporicidal activity The testprotocol specifies a contact time (see Table 23.0-1). Bovine serum albumin (BSA) is added as theinterfering substance at 0.3% to simulate clean conditions and 3.0% to simulate dirty conditions.
  - 第一步：悬液检验以确定杀菌、杀霉菌杀病毒或杀孢子活性。检验方案规定了接触时间（见表23.0-1）。加入0.3%牛血清白蛋白（BSA）作为干扰物质以模拟清洁环境，加入3.0%的牛血清白蛋白以模拟脏环境。
  - Step 2: Tests attempting to simulate practical conditions, for example, surface tests.
  - 第二步：模拟实际情况的检验，如表面检验。
- Phase 3: Field trial tests (in-situ field studies).
- 阶段3：现场试验（实地研究）

The following list describes the typical EN tests currently used by vendor companies evaluating disinfectantsfor registration purposes:

以下列表描述了当前供应商公司以注册为目的用于评价消毒剂常用的EN检验：

- EN 1276:2009 Chemical disinfectants and antiseptics.
- EN 1276:2009 化学消毒剂和防腐剂

Quantitative suspension test for the evaluation of bactericidal activity of chemical disinfectants andantiseptics used in food, industrial, domestic, and institutional areas (phase 2, step 1).

用于评价食品、工业、家庭、公共领域用化学消毒剂和防腐剂杀菌活性的悬液定量试验（阶段2，第一步）

- EN 1650:1998 Chemical disinfectants and antiseptics.
- EN 1650:1998化学消毒剂和防腐剂

Quantitative suspension test for evaluation of fungicidal activity of chemical disinfectants and antisepticsused in

food, industrial, domestic, and institutional areas (phase 2, step 1).

用于评价食品、工业、家庭、公共领域用化学消毒剂和防腐剂杀真菌活性的悬液定量试验（阶段2，第一步）

- EN 13704:2002 Chemical disinfectants.
- EN 13704:2002 化学消毒剂

Quantitative suspension test for the evaluation of sporicidal activity of chemical disinfectants usedin food, industrial, domestic, and institutional areas; test method and requirements (phase 2, step 1).

用于评价食品、工业、家庭、公共领域用化学消毒剂杀孢子活性的悬液定量试验；试验方法和要求（阶段2，第一步）

- EN 13697:2001 Chemical disinfectants and antiseptics.
- EN 13697:2001化学消毒剂和防腐剂

Quantitative nonporous surface test for the evaluation of bactericidal or fungicidal activity ofchemical disinfectants used in food, industrial, domestic, and institutional areas (phase 2, step 2).

用于评价食品、工业、家庭、公共领域用化学消毒剂杀菌或杀霉菌活性的无孔表面的定量试验（阶段2，第二步）

A brief overview of the criteria for each EN test is outlined in the table that follows:

每个EN检验的标准小结见下表：

Table 23.0-1 Summary of EN Test Criteria for Registration for Established Claims

表23.0-1 已制定的声明进行注册用的EN检验标准总结

Organism type 生物类型	Test Method 检验方法	Test Type 检验类型	Contact Time (minutes) 接触时间（分钟）	Log Reduction Pass Criteria 对数下降合格标准
Vegetative bacteria 细菌繁殖体	EN 1276:1997	Suspension 悬液	5	5
Vegetative bacteria 细菌繁殖体	EN 13687:2001	Surface 表面	5	4
Vegetative fungi 霉菌繁殖体	EN 1650:1998	Suspension 悬液	15	4
Vegetative fungi 霉菌繁殖体	EN 13697:2001	Surface 表面	15	3
Bacterial spores 细菌孢子	EN 13704:2002	Suspension 悬液	60	3

Users' Protection: Safety Data Sheets (SDS)

使用者的防护：安全数据表（SDS）

Wearing gloves is a critical safety procedure when handling and using sanitizers, disinfectants, and sporicides. Typically rubber or nitrile gloves are recommended for the hands, as well as chemically compatible gowning materials, when diluting or using disinfectants. Operators that are applying thedisinfectants to ceilings should wear hoods or smocks and goggles with an ocular cavity fit so that the disinfectant or sporicide does not get into the ocular cavity. Generally, a rubber apron should beused when diluting a disinfectant product. Finally, sporicides and alcohol products should be used in well-ventilated areas, or a breathing apparatus should be used, to prevent overexposure to any volatile actives.

处理和使用杀菌剂、消毒剂和杀孢子剂时戴手套是一种关键的安全措施。在稀释或使用消毒剂时，通常推

荐戴橡胶或丁腈手套，也推荐化学相容的衣服材料。将消毒剂用在屋顶上的操作工应戴兜帽或穿罩衫并戴与眼周围贴合的防护眼镜以使消毒剂或杀孢子剂不会进入眼内。通常在稀释消毒剂产品时会穿橡胶围裙。最后，杀孢子剂和乙醇产品应当在具有良好通风的环境下使用或应用时佩戴呼吸装置，以避免过度暴露于任何挥发性活性物质中。

In the United States, the Safety Data Sheets (SDS) and Environmental Protection Agency (EPA) registeredlabels, as well as any additional toxicological studies from the vendor, are the primary source for additional safety information. See Appendix V (Section 21.0) for the EPAs safety labeling requirements.

在美国，安全数据表（SDS）和环境保护局（EPA）注册的标签，以及供应商的任何额外的毒理研究都是进一步的安全信息。EPA安全标签要求见附录V（21.0部分）。

Companies that are considering fogging a disinfectant or a sporicide should be sure to have adequate ventilation or ancillary breathing apparatus while applying in the clean room before operators return to their workstations. The levels of the active in the clean room should be below permissible exposurelimits before operators return to their workstations.

考虑消毒剂或杀孢子剂雾化使用的公司应确保在洁净室使用时，操作人员返回工作岗位前有足够的排风或辅助呼吸装置。在操作人员返回工作岗位之前洁净室内的活性成份的量应低于允许暴露限度。

The individual firm is responsible for complying with environmental, health, and safety regulationsfor disposal, storage, and personnel protection within the laws of their respective countries, states,cities, counties, and townships. Regulations may vary between authoritative bodies within a region, and appropriate due diligence should be exerted to meet all federal, state, and local requirements.

每个公司应符合其所有国家、州、市、县和镇的法律中的关于处置、贮存和人员保护的环境、健康和安全规定。在一个区域内的不同权威机构的规定可能会不同，应进行适当的尽职审查以符合所有的联邦、州和地方的要求。

24.0 Appendix VIII: Large-Scale

附录 VIII：大规模

Gassing Or Fogging Of Clean Rooms

洁净室的气体或雾化处理

Vaporization or fogging of disinfectants for large-scale decontamination is being used or consideredby many firms in the pharmaceutical industry. A significant amount of published data show the efficacy of this type of disinfectant system against vegetative bacteria, fungi, and bacterial spores. Chemicalagents commonly used for this technology include the following:

制药工业的许多公司都采用或考虑采用消毒剂的汽化或雾化来进行大规模的消毒。大量的已发布数据显示这种类型的消毒系统对细菌繁殖体，霉菌繁殖体和细菌孢子有效。这项技术所常用的化学剂如下：

- Paraformaldehyde
- 多聚甲醛
- Peracetic acid/hydrogen peroxide
- 过氧乙酸/过氧化氢
- Phenols
- 酚类
- Bleach
- 漂白剂
- Quaternary ammonia
- 季铵盐类
- Vapor phased hydrogen peroxide (VHPH)
- 过氧化氢蒸汽
- Gaseous chlorine dioxide
- 气态二氧化氯
- Ozone
- 臭氧

While gassing and fogging systems can provide excellent destruction of microorganisms present in areas that are contaminated, such systems do not clean surfaces. Therefore, cleaning is considered to be a mandatory and routine step in addition to gassing or fogging.

尽管汽化或雾化系统能对受污染的区域中存在的微生物实施强有力的杀灭，但是这些系统并不能清洁表面。因此，除了汽化或雾化之外，清洁也被认为是一个强制的和常规的步骤。

- Paraformaldehyde
- 多聚甲醛

Paraformaldehyde gas has been used as a large-scale clean room decontamination methodologyfor many years. Paraformaldehyde is a white, crystalline powder with the odor of formaldehydethat has been used for more than thirty years to decontaminate laboratory facilities and to disinfect sickrooms, clothing, linen, and sickroom utensils. The process involves heating of the paraformaldehydeto release formaldehyde gas, which is the actual decontaminant. (See http: //www.epa.gov/pesticides/factsheets/chemicals/paraformaldehyde_factsheet.htm for more information)

多聚甲醛气体用做大规模的洁净室消毒已有多年。多聚甲醛为一种白色结晶性粉末，有甲醛的气味，用于试验室、病房、衣物、亚麻织物和病房用品的消毒已经超过三十年。操作过程为将多聚甲醛加热，释放出甲醛气体，它是实际的消毒剂（更多信息参见http: //www.epa.gov/pesticides/factsheets/chemicals/paraformaldehyde_factsheet.htm）

The gas is created inside the room, normally by use of a pan and a heating element. The gas isthen spread throughout the room by portable fans that are set up prior to the creation of the gas.

此气体在室内产生，通常使用一个平锅加热。然后通过放置在气体发生部位之前的便携式风扇将气体分散到整个房间。

Paraformaldehyde gas microbial destruction claims through the U.S. EPA are limited to what would be termed a high-level disinfectant, sanitizer, or fungicide. However, as with many other agents, sporicidal reduction has been obtained in clean rooms by many firms worldwide.

美国EPA批准的对多聚甲醛气体的微生物杀灭声明限于应将其称为一种高级的消毒剂、杀菌剂或杀霉菌剂。然而，通过使用许多其它的消毒剂，世界上很多公司也能够在洁净室内减少孢子的量。

While effective, Paraformaldehyde is an older methodology that has been replaced by most GMPfirms with current more modern chemistries and systems. Characteristically, Paraformaldehydedecontamination leaves concerning residuals on all surfaces (as defined by FDA) and requires the utmost safety concerns for its implementation realting to human health. For these reason this methodologyis declining in use in the marketplace.

尽管有效，多聚甲醛也是一种较古老的方法，已经被大多数GMP公司用目前较现代的化学法和系统所取代。FDA提出，多聚甲醛消毒时特征性地在所有表面上有残留，并且要求最大限度地考虑其使用时影响到人体健康的安全性问题。由于这些原因，此方法在市场上的使用逐渐减少。

- Wet Droplet Fogging 湿滴雾化

Wet droplet fogging has been employed in a variety of industries for many years and is a proven technology. This method involves the generation or vaporization of small liquid droplets from achemical agent that is placed into an air steam by a generator that is linked to a fogging device.

湿滴雾化广泛用于行业中已有多年，是一种成熟技术。这个方法为将一个发生器与雾化装置相连，发生器将化学剂形成或汽化成小液滴放到气流中。

Droplets usually range in size from 10.0 to 25.0 microns. The chemical agent is slowly dripped intothe stream of air in the fogging device. Various fogging devices are placed strategically throughoutthe room, and portable fans are used to circulate the droplets throughout the room. Chemicalagents such as peracetic acid and hydrogen peroxide, sodium hypochlorides, phenols, and quaternaryammoniums are normally used and chosen based on the type of antimicrobial action that is required.Efficacy is based on the fogging time and the chemical agent used. The method is versatile, as end users can decide on what agent and what fogging time should be employed. Antimicrobial claims can range from sanitization to sporicidal, depending on the chemical agent used, and have been obtained by both registering companies and GMP forms worldwide.

液滴粒径范围为10.0到25.0微米。化学剂缓慢滴入到雾化装置内的气流中。按照一定的策略将多个雾化装置分布在房间内，用便携的风扇来使液滴在整个房间内流通。通常使用的化学剂为过氧乙酸和过氧化氢、次氯酸钠、酚类和季铵盐，根据所需的抗微生物的作用来选择。其效力取决于雾化时间和所使用的化学剂品种。此方法是通用的，因为最终用户可以决定使用哪种消毒剂，多长的雾化时间。根据所用的化学剂，抗微生物声明可以在灭菌剂到杀孢子剂的范围内，并且已经由注册公司和世界各地的GMP公司获得。

The goal of the fogging method is to lightly coat all surfaces with a thin but constant layer of chemicalagent for an extended period. This type of decontamination is considered a wet or aerosol process ratherthan a gaseous process. Wetting of surfaces reduces decontamination times, dry times, and release times. Normal fogging times range from fifteen minutes to one hour, and release times are normallyvery short, also ranging from fifteen minutes to one hour, or when all surfaces are dry Once inhalation concerns are acceptable, end users could enter areas and dry any surfaces that are not completely dried.

雾化方法的目标是用化学消毒剂将所有表面轻易地包被非常稳固的一薄层并持续很长时间。这种类型的消毒被认为是湿法或气溶胶方法，而不是气化方法。润湿表面可以减少消毒时间、干燥时间和释放时间。通常的雾化时间范围为15分钟到一小时，释放时间通常非常短，范围也在15分钟到一小时，或者当所有表面都变干后。一旦达到可接受的吸入标准，最终用户就能够进入到区域内并且将所有未完全干的表面弄干。

But this should be done with the utmost concern for contamination of such surfaces.

但是这应当在充分考量后不会污染这些表面的情况下进行操作。

Depending on the chemical agent used, corrosion and residual can be controlled. However, with overuse and without manual cleaning procedures, residues can build up over time and corrosion can occur.

根据使用的化学消毒剂，可以对腐蚀和残留进行控制。然而过度使用和没有人工清洁方法时，残留的消毒剂会过久停留，会发生腐蚀。

- Vaporized Phased Hydrogen Peroxide (VPHP) 过氧化氢蒸汽（VPHP）

The vapor of hydrogen peroxide is noncarcinogenic and breaks down to water and oxygen, thereforeeliminating corrosive residues that are inherent with other traditional methods of large-scaledecontamination such as paraformaldehyde gassing.

过氧化氢蒸汽不致癌，分解成水和氧气，因此，不存在其它大规模消毒的传统方法固有的腐蚀残留物，如多聚甲醛气化。

VPHP systems generate a low level of vaporized 35% hydrogen peroxide (250-1200 ppm) intomanufacturing areas through portable or fixed distribution systems. In the vapor phase, disinfectionmay require longer times compared to the traditional method, depending on the number of VPHPgenerators, the size of the area to be treated, and the required contact and clearance times. Vaporis continuous is emitted through dispensing heads in an attempt to distribute the vapor and provide sufficient vapor in all areas to destroy microorganisms.

通过固定式或便携的分配系统，VPHP系统产生的少量35%过氧化氢蒸汽(250-1200 ppm)释放到生产区域中。与传统方法相比，在汽化阶段，可能需要更长的时间消毒，这取决于使用的VPHP发生器数量，被消毒的区域大小和所需要的接触和清洁时间。蒸汽通过分配头连续散发出使其尽量分布到所有区域并提供足够的蒸汽以消灭微生物。

The distribution of vapor within the room can be verified with hydrogen peroxide sensors or chemicalindicators.

可以通过过氧化氢探头或化学指示剂证实房间内蒸汽的分布。

The VPHP process of decontamination, while effective, is still considered a disinfection step ratherthan a sterilization process. Implementing this type of disinfection system should be done with appropriate safety

precautions. Leaks to the external environment and clearance time should be tested and assessed properly to assure safety. The VPHP system may require air-handling systems to be shut off and doorways and return vents sealed. Release times for human intervention mayrun from two to four hours, depending on the size of the area and the length of the gassing process.

VPHP消毒过程，虽然有效，但是仍被视为一种消毒过程而不是灭菌过程。应在适当的安全警告措施下实施这类的消毒。应检验对外界环境的泄漏和清除时间并正确评估以确保安全。VPHP系统要求空调系统关闭，门口和回风密封。可允许人员干预的释放时间为2到4小时，取决于区域的大小和气化过程的长短。

The effectiveness of VPHP systems has been well documented in isolator operations for manyyears. However, isolator operations are smaller, are sealed, and have evacuation systems that canremove and scrub the volatile gases. The use of VPHP in a large-scale, open manufacturing environment has also been very successful and unlike UV is effective in the presence of shadowing.

多年来，VPHP系统的有效性已经在隔离器操作中得到很好的文件证明。然而，隔离器操作空间较小，密封，并且有能够除去并净化挥发性气体的排出系统。在大规模开放的生产环境中使用VPHP也已经非常成功并且不像UV那样，VPHP对有阴影的区域也有效。

However, conclusive studies proving validation of the system in this venue are specific to the operationand the setup where it will be used. Each area should be assessed for effectiveness in its ownvalidation study. Although large-scale VPHP has proved effective, it is not a cleaning step. Residues,particulates, foreign matter, and pyrogens are not cleaned or removed from the environment in theVPHP process. Therefore, routine cleaning of surfaces and equipment is considered mandatory even when VPHP is used. VPHP then serves as an additional bioburden reduction step either before or after cleaning. A large-scale VPHP system used before cleaning would be considered a sanitization step and should be followed by a mechanical-action (wipe and mop) application to the surface.

但是，证明在这个地点内此系统的验证的决定性的研究是专门针对操作和使用区域内的设置的。每个区域都应当在其自身的验证研究中评价其有效性。尽管证明了大规模VPHP是有效的，但是它并不是一个清洁步骤。在VPHP过程中残留、粒子、异物和热原不会从环境中除去。因此，尽管使用VPHP，常规的表面清洁和设备清洁仍被认为是强制性的。无论是在清洁前还是在清洁后，VPHP是一种额外的降低生物负荷的步骤。在清洁前使用大规模VPHP系统将被认为是一个卫生（sanitization）步骤，应当随后在表面上实施一个机械作用（擦拭和用拖布拖）。

A large-scale VPHP system that is implemented after a mechanical cleaning step (wipe and mop)would be considered a final disinfection step.

机械清洁步骤（擦拭和用拖布拖）之后实施的大规模VPHP系统被认为是一个最终的消毒（disinfection）步骤。

- Gaseous Chlorine Dioxide 气态二氧化氯

Gaseous chlorine dioxide is another available alternative for gassing. Of the methods already discussed,it is most similar to paraformaldehyde or VPHP rather than wet droplet fogging, as it is agas product. Application to the area to be decontaminated and to the surface is accomplished much the same way as the VPHP gas processes. Basic differences in the products relate to corrosion, residual,safety, and setup.

气态二氧化氯是另一种备选的气体处理方式。在已经讨论的所有方法中，这个方式与多聚甲醛或VPHP最为相似，而不是湿滴雾化，因为其为气体产物。与VPHP气体过程相同的方式在待消毒区域和表面上使用。两产品的基本区别在腐蚀、残留、安全和设置方面。

To disinfect a room, gaseous chlorine dioxide is precipitated into the area to be decontaminated via a generator and

dispersion heads. These systems have been employed in many industry settings and are now being considered as a possible alternative for GMP operations.

要消毒一个房间，则使用一个发生器和分散头将气态二氧化氯沉淀在待消毒区域内。这个系统已经在多个产业环境内使用，并且现在正在被考虑作为GMP操作中可能的备选。

- Ozone Gas 臭氧

The use of Ozone Gas ia another alternative for gassing small or large scale operations. Ozone ismade by adding high voltage to oxygen. The system uses a high concentration of ozone gas that bintegrates a gas generator to emit the Ozone to the area to be decontaminated. Normally the design specifications for the system included an ozone gas concentration of 200 ppm or more,relative humidity of 80% or more, and a treatment time that is determined by the size of the area,the inherent bioburden and the obstructions contained within the area. These systems have beenemployed in many industry settings and are now being considered as a possible alternative for GMPoperations.

用气体处理小范围或大规模操作可选的另一种方式是使用臭氧。臭氧是通过氧气加高电压制成。该系统使用了高浓度的臭氧气体，集成一个气体发生器向待消毒区域内释放臭氧。该系统的设计规范通常为臭氧浓度200ppm或更高，相对湿度80%或更高，处理时间取决于区域的大小，自身的生物负载和区域内的障碍物情况。这个系统已经在多个产业环境内使用，并且现在正在被考虑作为GMP操作中可能的备选。

Whenever chemical agents are used for large-scale gassing or fogging of clean rooms, safety concernsmust be addressed. All of the agents discussed can result in injury or death of personnel if proper precautions are not taken to ensure the containment of the chemical agent to the intended areas.

每当化学剂用于大规模气体处理或雾化处理洁净室时，必须考虑安全性。如果未采用正确的防范措施来保证化学消毒剂被遏制在拟处理区域范围内，那么所讨论的所有消毒剂都能够导致人员的伤害或死亡。

For many of the agents discussed, residues that are left behind on product-contact surfaces are also a significant concern and must be evaluated.

对于所讨论的大部分消毒剂而言，在与产品接触表面的残留物也是一个重要问题，必须评估。

Although these methods of decontamination are effective, they should not be used to replace a routine program for cleaning and disinfecting the clean room areas. If they are used as the standard practice,they should be validated to demonstrate their ability to achieve an appropriate level of bioburden reduction. This should be performed taking into consideration the material of construction present in the clean room areas.

尽管这些消毒方法是有效的，然而它们不能取代清洁和消毒洁净室区域的例行程序。如果它们作为标准实践使用，那么应当对其进行验证以证明它们能够使生物负载降低适当水平。实施这个验证时应当将洁净区内的构造材质考虑在内。

It is also important to consider the source of these organisms, for gassing will only remove what is present and may leave behind moisture, allowing for further proliferation if the causative agents havenot been removed from the area.

同样重要的还有考虑这些生物体的来源，因为气体处理只能除去存在的生物体，并会留下湿气，如果病原体没有从区域中除去，会使得其进一步增殖。

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