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Recommended Practices for Manual Aseptic Processes

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PDA Recommended Practices for Manual Aseptic Processes Technical Report Team

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Table of Contents

TABLE INDEX

1.0 Introduction
简介

The purpose of this technical report is to outline methods and approaches for control and evaluation of aseptic processing operations for drug products/medicinal products which use all or partially manual procedures. The goal of aseptic processing is to prevent the contamination of sterile materials during their processing. The goal of evaluating any aseptic process is to demonstrate that aseptic processing can be achieved and maintained successfully under the specified operational configuration, activities, and conditions. These goals are the same for manual or automated aseptic operations, and for small-scale or large-scale operations.

这份报告的目的就是介绍用于评价和控制全部使用或部分使用手动操作生产的药品和医疗用品的无菌操作过程的方法。无菌操作的目的是阻止无菌物料在工艺过程中不会污染。评估无菌操作的目的就是为了证明通过规定的操作配置、行为和条件，能够成功实现并维持无菌工艺。这些目标对于人工操作、自动操作，大批量小批量操作都是一样的。

Manual aseptic processing (MAP) operations differ from automated operations in several ways. These differences pose unique operational and evaluation challenges not generally encountered with automated operations. These challenges must be considered thoroughly when designing the evaluation procedure or protocol for the MAP operation. MAP involves a human operator performing, at a minimum, the container and/or closure movements. Some semi-automated equipment may be used, but the process is not fully automated. For this reason MAP relies heavily on individual operators basic understanding of microbiology proficiency where personnel must be individually qualified.

MAP 操作在几个方面不同于自动操作。这些不同引起独特的操作和评估的挑战，这些挑战在自动操作时不会遇到。这些挑战在设计评估 MAP 操作的方案或程序的时候就要充分考虑。MAP 包括人员操作，最少包括容器、瓶盖的移动。一些半自动的设备可能被用到，但过程不是完全自动的。因此，MAP 很依赖操作人员个人对于微生物学的理解，这些人必须考核合格。

The greatest source of microbial contamination during MAP is generally recognized to be the operational personnel and their activities. Aseptic processes that rely on manual operations are inherently subject to performance or procedural drift over time. Furthermore, reproducible human performance cannot be assumed, especially where there are significant time gaps between aseptic processing events. The likelihood of human performance deviations or failures is linked to:

MAP 过程中最大的污染源一般被认为是人员及人员行为。依赖人工操作的无菌工艺本质上取决于随着时间变化的操作行为或程序。而且，不能嘉定人员操作时可重复的，尤其是在无菌工艺事件之间有长的时间间隔时。人员操作偏差或失败的可能性与以下相关：

- Complex aseptic processing tasks
  无菌工艺任务的复杂性
- The continuous span of time during which an operator carries out repetitive aseptic activities
  操作人员执行重复的无菌操作的持续时间
- The expected rate of activity
  活动的频率
- Change in personnel
  人员的变更

This technical report has value for hospital and formulation pharmacies where manual aseptic processing may occur. The guidance provided in this report may be applicable to various operations, including: vaccine preparation, cell culture, gene therapy, IND/IMP manufacturing, clinical and commercial manufacturing, and pharmacy formulation and dispensing. When manual aseptic processing of sterile dosage forms is required, special consideration must be given to sterility and verification of processing accuracy, as the administration of these products into the vascular and nervous system of human subjects poses the greatest risk of harm. As applicable, the 2004 FDA guidance on aseptic processing, EU GMP-Annex 1, Ph Eur 5.1.1, and USP Chapters <797> and <823> provide procedures and the requirements for (*1-5):*
这个技术报告可以用于进行可能进行人工无菌工艺的医院和药厂。报告中的指南可以用于多种操作，包括疫苗制备、细胞培养，基因治疗，IND/IMP 生产，临床和商业生产，制药配药和分发。当无菌制剂生产过程要求无菌工艺时，因为这类产品注射进入血管和神经系统会造成最大的伤害，尤其要注意无菌和工艺准确性的确认。2004FDA 无菌指南，EUGMP 附录一，欧洲药典 5.1.1 和 USP797 和 823 提出程序和要求：

- Training of personnel involved in sterile preparation processes
  涉及无菌产品生产的人员的培训；
- Environmental control and monitoring requirements
  环境控制和监控
- Specifications for sterile and non-sterile ingredients and components
  无菌和非无菌原辅料、材料的标准
- Release criteria for sterility and pyrogen testing
  无菌和热原测试的放行标准

Compliance with these requirements is paramount to ensure the safety of human recipient.
符合这些要求主要是为了保障用药人的安全。

Some of these processes require aseptic steps subsequent to sterilization but prior to filling, such as volume or pH adjustments, which present their own contamination risks.
一些工艺要求在灭菌后灌装前进行无菌操作，例如装量和 pH 调整，他们会引入自身的污染风险。

This report is not intended to address the brief, relatively infrequent, human interventions into an otherwise automated filling process. Examples include reach-ins to remove a toppled vial from the filling line or to obtain a container for a fill-weight check, aseptic connections made during set-up, corrective activities during line stoppages, and so on. Operator activities and interventions of this nature should be integrated into the aseptic process simulation (APS) of the respective automated processes and they will not be addressed further in this report ***(6).***
这个报告不包括一些简单的相对较少的对于自动灌装工艺的人员干扰。例子包括伸进去取一个灌装线上斜了的瓶子或者去用于灌装装量测试的容器，安装时候的无菌连接，加塞过程的纠正行为，等等。操作人员这类的行为和应该在各自自动工艺的无菌工艺模拟中进行，不会在这个报告中进一步说明。

The guidance provided in this report builds upon, and is intended to supplement, published guidance which is generally more focused on automated large-scale operations. The list of references at the end of this

report includes sources upon which this report is based.
这个报告建立在已发布的更侧重于自动的大规模操作指南的基础上，并进行补充。参考资料清单包括报告的基础来源。

In conclusion, for adequate evaluation of the manual aseptic process it is important that human factors, such as those described above, are fully accounted for in both the design of an MAP and also in the design of the APS program. The sections that follow include points to consider in that evaluation.
总之，要足够的评价人工无菌操作，人员因素，包括所有上述内容，在 MAP 设计和 APS 项目中都要充分考虑。下面几部分内容包括评估中应考虑的要点。

2.0 Glossary of Terms
专业术语

Aerobic Microorganism：A microorganism that utilizes oxygen as the final electron acceptor during metabolism; a microorganism that will grow primarily in the presence of oxygen. For the purpose of this report, this definition encompasses facultative anaerobes ***(6).***
需氧菌：需要用氧气最为最终电子接受体的微生物；主要在有氧环境下生长的微生物。对于本报告，这个定义包括兼性厌氧菌。

Anaerobic Microorganism：A microorganism that does not utilize oxygen as the final electron acceptor during metabolism; microorganism that will grow only in the absence of oxygen ***(6).***
厌氧菌：不需要用氧气作为追中电子接受体；只能在无氧条件下生长。

Aseptic Filling：The part of aseptic processing where a pre- sterilized product is filled and/or packaged into sterile containers and closed ***(6).***
无菌灌装：无菌工艺的一部分，提前灭菌的药物灌装或包装到无菌容器并密封。

Aseptic Processing：Handling sterile materials in a controlled environment, in which the air supply, facility, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels ***(6).***
无菌工艺：在控制的环境中传递物料，在这个环境中，空气、厂房、物料、设备和人员要将微生物和尘埃粒子控制在可接受的范围内。

Aseptic Processing Area (APA)：Controlled environment, consisting of several zones, in which the air supply, facility, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels ***(6).***
无菌操作区：控制环境，包括几个区域，在这些区域空气，厂房，材料，设备，人员规范要求来控制微生物和尘埃粒子污染达到可接受水平。

Aseptic Processing Simulation (APS)：A means for establishing the capability of an aseptic process as performed using a growth medium. **Note:** Aseptic processing simulations are understood to be synonymous with media fills, simulated product fills, broth trials, broth fills, etc ***(6).***
无菌工艺模拟：用培养基来确立无菌工艺的容量。备注：无菌工艺模拟可以认为与培养基灌装，模拟产品灌装，肉汤试验，肉汤灌装等。

Barrier System：A system of physical partitions that affords ISO 5 protection by partially separating its interior from the surrounding environment utilizing airflow ***(6).***
隔离系统：物理隔离系统，通过采用气流将内部和外部环境分开来挺空 ISO5 的保护。

Bioburden：Total number of viable microorganisms on or in a health care product prior to sterilization ***(6).***
生物负荷：灭菌前在用于健康的产品表面或内部的活的微生物的总数量。

Biological Safety Cabinet (BSC)：An enclosed, ventilated workspace with engineering controls designed to remove or minimize exposure to hazardous biological materials. A BSC is a principle device to provide

containment of infectious splashes or aerosols generated by many microbiological procedures. BSCs are designed to provide personnel, environmental and product protection when appropriate practices and procedures are followed. A cabinet that is designed to protect the operator and the environment from the hazards of handling infected material and other dangerous biological *(7)*.
生物安全柜：一种封闭的、通风的工作区，它通过动力控制来移出或减少有害的生物物质的暴露。生物安全柜是一种重要的设备能够将许多微生物程序中产生的传播性的斑点或者颗粒控制其中。BSCs 用于提供人员、环境、产品保护，当还有后续合适的操作和程序。它是一个用于保护操作者和环境原理传递污染的物料和其它生物危险的风险。

Campaign：A series of consecutive production batches manufactured without intervening cleaning and sterilization ***(6).***
阶段生产：一系列连续的生产批次中间不用干扰性的清洁和灭菌。

Colony Forming Unit (CFU)： One or more microorganisms that produce a visible, discrete growth entity on a semi-solid, agar-based microbiological medium *(6)*.
CFU：在半固体、琼脂为主的微生物培养基上的一个或多个微生物形成的可见的、聚集的生长菌落。

Compounding：A process wherein bulk drug substance is comcombined with one or more excipients and/or another bulk drug substance to produce a drug product ***(6).***
配制：原料与一种或多种辅料或/和其它原料结合来生产一种药品。

Critical Area： An area designed to maintain sterility of sterile materials. Sterilized product, containers, closures, and equipment may be exposed in critical areas ***(6).***
关键区域：用于维持无菌物料的无菌性的区域。灭菌后的产品，容器，盖子和设备应该暴露在关键区域。

Environmental Monitoring Program：Defined documented program that describes the routine particulate and microbiological monitoring of processing and manufacturing areas. **Note:** The program should reference a corrective action plan in cases where action levels are exceeded ***(6).***
环境监控项目：确定的书面程序，它描述了在工艺生产区域常规的尘埃粒子和微生物监测。备注：这个项目需要有一个针对行动限超标的改正方案。

First Air (First Work Location)： The work location first in the path of HEPA filtered air (S).
初始气流：在经高效过滤器的气流路径中最开始的工作位置。

HEPA filter： High efficiency particulate air filter with minimum 0.3 j.im particle retaining efficiency of 99.97 percent (%).
高效过滤器：高效空气过滤器 0.3um 粒子的最小截留率 99.97%。

Human Factors：A science discipline that examines human psychological, social, physical, and biological characteristics to evaluate the design, operation, or use of products or systems for optimizing human performance, health, safety, and/or habitability ***(9).*** **[Synonym:** Ergonomics]
人员因素：为了优化人员操作、健康、安全和/或习惯，通过检查人员心理、社会的、身体的和生物学的特征来评价产品或系统的设计、运行或使用的科学原则。

Intervention： An aseptic manipulation or activity that occurs within the critical area. This technical report regards interventions as either corrective or inherent ***(6).***
干预：关键区域发生的无菌操作或行为。本报告提及的干扰既包括改正的和常规的干扰。

Intervention, Corrective： An intervention that is performed to correct or adjust an aseptic process during its execution. Examples include such activities as: clearing component misfeed, adjusting sensors, and replacing equipment components ***(6).***
纠正型干预：用于改正或调整无菌工艺的执行过程的干扰。例子包括：清空送错的组件，调整探头和重装设备组件。

Intervention, Inherent： An intervention that is an integral part of the aseptic process and is required for set-up or routine operation and/or monitoring, e.g., aseptic assembly, container replenishment, environmental sampling, etc. Inherent interventions are required by batch record, procedure, or work instruction for the proper conduct of the aseptic process ***(6).***
常规干预：作为无菌工艺整体一部分的干扰，装机或常规操作和/或监测，例如无菌安装，容器补充，环境取样等。固有的干扰操作在批记录、程序或者工作手册中要求。

ISO 5: Environmental operating conditions defined in ISO 14644-1, "Cleanrooms and associated controlled environments." Note: For total particulates, ISO 5 approximates the Class 100 description from the now obsolete U.S. Federal Standard 209, and is roughly comparable to Grade A as defined in European GMP Annex ^"Manufacture of Sterile Medicinal Products" ***(6).***
ISO 5：ISO14644-1 中定义的环境操作条件，洁净室和相关的控制环境。备注：对于总的粒子数，ISO5 与现在废除的美国联邦标准209中规定的100级类似，与欧洲GMP附录一中定义的A级大概一样。

ISO 7: Environmental operating conditions defined in ISO 14644-1, "Cleanrooms and associated controlled environments." Note: For total particulates, ISO 7 approximates Class 10,000 from the now obsolete Federal Standard 209.
ISO 7：ISO14644-1 中定义的环境操作条件，洁净室和相关的控制环境。备注：对于总的粒子数，ISO7 与现在废除的美国联邦标准 209 中规定的 10000 级类似.

ISO 8: Environmental operating conditions defined in ISO 14644-1, "Cleanrooms and associated controlled environments." **Note:** For total particulates, ISO 8 approximates Class 100,000 from the now obsolete Federal Standard 209.
ISO8：在 ISO14644-1 中要求的环境操作条件，洁净室和控制的环境。备注：对于总的粒子，ISO 接近现已废除的联邦标准 209 的十万级。

Isolator, Closed： A decontaminated unit meeting ISO 5 conditions that provides uncompromised, continuous, isolation of its interior from the surrounding environment. Any air exchange with the surrounding environment takes place only through microbially retentive filters ***(6).***
密闭式隔离器：一种降低污染的装置满足 ISO5 的条件，它的内部能够不受影响的、连续的、与外部隔离。与外部进行气体交换只通过微生物截留滤芯。

Isolator, Open： A decontaminated unit meeting ISO 5 conditions that provides uncompromised,

continuous isolation of its interior from the surrounding environment. It may transfer air directly to the surrounding environment through openings (e.g., "mouseholes") that preclude the ingress of microbial contamination ***(6).***
开放式隔离器：一种降低污染的装置满足 ISO5 的条件，它的内部能够不受影响的、连续的、与外部隔离。它直接通过老鼠洞将空气传送到外部环境中以此来避免微生物污染。

Positive Unit：Unit filled in an aseptic processing simulation that exhibits detectable microbial growth after incubation ***(6).***
阳性单元：无菌工艺模拟时灌装的单元，培养后里面有可见的微生物生长。

Restricted Access Barrier System (RABS)：RABS are aseptic processing systems (ISO 5) intended to substantially reduce human borne contamination within the aseptic environment where sterile product, containers, closures and equipment are exposed by the use of separative devices and defined mechanical features and operating procedures ***(6).***
RABS 系统：RABS 是无菌工艺系统用于显著降低无菌环境中人员携带的污染，通过它无菌产品、容器、盖子、设备利用特别的装置、确定的机械性能和操作程序处理。

Shift：Scheduled periods of work or production, usually less than 12 hours in length, staffed by alternating groups of workers ***(6).***
班次：工作或生产的计划周期，一般小于12小时，通过人员变化来提供工作人员。

Sterile：Absence of life; usually refers to absence of viable microorganisms. Note: In practice, no such absolute statement regarding the absence of microorganisms can be proven (see "Sterilization") ***(6).***
无菌：无生命；通常指无活的微生物。备注：实际上，没有能被证明的绝对的无微生物。

Sterility Test：Test performed to determine if viable microorganisms are present ***(6).***
无菌测试：用来确定是否有活的微生物的测试。

Sterilization：Validated process used to render a product free of viable microorganisms.
Note: In a sterilization process, the nature of microbiological death or reduction is described by an exponential function. Therefore, the number of microorganisms which survive a sterilization process can be expressed in terms of probability. While the probability may be reduced to a very low number, it can never be reduced to zero ***(6).***
灭菌：验证过的工艺用来保证产品无活菌。
备注：灭菌工艺中，微生物的死亡率或降低率用指数形式表示。因此，灭菌工艺残留的微生物的数量用可能性来表示。

Validation：Establishing documented evidence that provides a high degree of assurance that a specific process will consistendy produce a product meeting its predetermined specifications and quality attributes.
Note: There has been wide-spread evolution in the concept and definition of validation in recentyears. Readers should refer to definitions established recently by the U.S. FDA, European regulators and other bodies in guidances and regualtions ***(6).***
验证：确定的书面证据用来提供高度的保证，保证一个特别的工艺能够持续生产出符合既定标准和质量参数的产品。

备注：最近几年关于验证的概念和定义有了很大的进步。读者需要参照USFDA、欧洲法规和其它指南和法规最近给出的定义。

Unidirectional Air Flow Hood (UAFH)：A cabinet designed to protect materials from operator and environmental contamination. Also referred to as laminar air flow hood.
单向层流罩：一个用于使物料免于人员和环境污染的柜子。

Worst Case：A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure ***(6)*.**
最差条件：包括工艺限值的上下限和环境的一一系列条件，包括哪些在标准程序要求范围内，能够最大可能引起工艺或产品失败的条件（与理想条件相比）。这些条件不是必然能够引起产品或工艺失败。

3.0 Buildings And Facilities
厂房与设施

The selection of an appropriate clean environment in which to perform the required manufacturing activities is critical to MAP operations. In general, the minimum requirement is an ISO 5 environment in which unidirectional air flow protection is provided to critical materials during the manufacturing procedures. A listing of selected air quality classification standards is shown in Table 3.0-1. In practice many different locations and equipment for MAP operations are possible, including:
选择合适的洁净环境来执行要求的生产操作对 MAP 来说很重要。一般来说，最低要求是 ISO5，在生产过程中这个环境能够对关键物料提供单向流保护。表 3.0-1 是选择的空气质量分级标准清单。实际上，可能使用许多不同的位置和设备来实现 MAP，包括：

- A portion of a larger environment of the same class
  同一级别的大环境中的一部分；
- A localized unidirectional air flow hood (also known as a laminar flow hood or I,AFH) protecting a specific portion/area within a lower classified environment
  局部单向层流罩（单向层流罩或 LAFH）在较低级别环境中来保护某一区域；
- A table mounted unidirectional air flow hood (with either horizontal or vertical air flow)
  装有层流的工作台（水平或垂直）
- An isolator (open or closed)
  隔离器（开放或封闭）

Table 3.0-1 Cleanroom Standards Airborne Particulate Limits (particles/m^3) *(10)*

ISO 14644	US FDA(Aseptic Processing Guidance)	USP <1116>	EU Annex 1 and WHO	Japan(Aseptic Processing Guidance)	JP XVI
ISO 5 ≥0.5 μm 3520 ≥5 μm 29	**ISO 5/Class 100**[1] 3520[2] Not specified	**ISO 5/Class 100**[1] 3520[2] Not specified	Grade A Grade B（at rest） 3520 20[3]	Grade A Grade B（at rest） 3520 20[3]	Grade A Grade B（at rest） 3520 Not specified
ISO 7 ≥0.5 μm 352,000 ≥5 μm 2,900	**ISO 7/Class 10,000** 352,000 Not specified	**Class 10,000** 352,000 Not specified	Grade B (operation) Grade C（at rest） 352,000 2,900	Grade B (operation) Grade C（at rest） 352,000 2,900	Grade B (operation) Grade C（at rest） 352,000 Not specified
ISO 8 ≥0.5 μm 3,520,000 ≥5 μm 29,000	**Class 100,000** 3,520,000 Not specified	**Class 100,000** 3,520,000 Not specified	Grade C (operation) Grade D（at rest）[4] 3,520,000 29,000	Grade C (operation) Grade D（at rest）[4] 3,520,000 29,000	Grade C (operation) Grade D（at rest）[4] 3,520,000 Not specified

1. Class 100 and Grade A are defined as requiring unidirectional flow by all applicable guidelines
   各类指南 100 级和 A 级要求单向流
2. Class titles for US FDA and USP indicate equivalent particle counts per ft^3
   US FDA 和 USP 分级的粒子计数单位为每 m^3
3. ISO 4.8 based upon reduced limit for particles ≥5 μm
   ISO 4.8 标准基于≥5 μm 的粒子限度降低

4. Grade D operational particulate counts are dependent upon the operation and are not defined by any guideline
   D 级动态粒子计数取决于操作，指南中没有定义。

Each of the above is in current use in the industry for the conduct of MAP operations. In general, as MAP operations become more complex, a more sophisticated and complex operating environment will be required. The manual processes considered in this report are commonly carried out in either a unidirectional air flow hood or an isolator. A unidirectional air flow hood (UAFH) is a cabinet designed to protect materials from operator and environmental contamination. All air supplied to the UAFH is High Efficiency Particulate Air (HEPA) filtered. In operation, all air flows from the UAFH, through the critical manufacturing areas, and exits to the surrounding environment.
上面列出的每一项都是 MAP 操作正在使用的。总体上，由于 MAP 越来越复杂，那么也要求更复杂的环境。本报告考虑的人工操作通常是在单向层流罩下或者隔离器中。单向层流罩（UAFH）是一种用于保护物料免于人员和环境污染的柜子。供给 UAFH 的空气都是经过高效过滤器（HEPA）过滤的。动态操作时，从 UAFH 出来的气流，经过关键生产区域，再回到周围环境中。

An isolator is a decontaminated system, meeting ISO 5 conditions, which provides uncompromised and continuous isolation of its interior from the surrounding environment. A closed isolator only allows air exchanges with the surrounding environment through microbially retentive filters. An open isolator may transfer air directly to the surrounding environment through openings (commonly called "mouse holes") that preclude the ingress of microbial contamination. All these environments provide appropriate conditions for the execution of MAP operations which are considered critical zones.
隔离器是一种降低污染的系统，满足 ISO5，能够将内部与周围环境有效的持续的隔离。封闭隔离器只通过微生物截留滤芯与周围环境进行空气交换。开放式隔离器可能通过开口（俗称老鼠洞）将空气直接排放到周围环境中，以防止微生物的聚集。这些提供了用于进行 MAP 操作条件的环境都是关键区域。

Biological Safety Cabinets (BSC) are designed to protect operators and the external environment from infected or dangerous materials inside the cabinet. All air to and from the BSC is HEPA filtered before entering the cabinet or exhausting to the external environment. Some BSC designs provide some measure of protection to the materials being handled. Since air flows into the BSC from the surrounding environment, biosafety cabinets should be used only when worker safety from the material being handled is a meaningful concern. Worker safety must also be considered if the toxicity of the compound has not yet been determined.
生物安全柜（BSC）用来保护操作者和外部环境免于柜中传染或危险物质。进出 BSC 的空气都是经过高效过滤器的。一些 BSC 设计用于保护被处理的物料。由于空气是从周围环境进入 BSC，所以只有当处理的物料影响工作人员安全时才应该使用生物安全柜。当化合物毒性尚未确定时也要考虑工作人员安全。

The supporting clean environment outside the critical zone is typically ISO 7 when a UAFH or BSC is utilized for the manual process. The use of an isolator under appropriate risk-management procedures may relax the requirements for the surrounding area; most new manufacturing installations employ an ISO 8 background environment in accordance with the 2004 FDA aseptic processing guidance (1) or European GMP Annex 1 ***(2)*.**

当使用 UAFH 或 BSC 时，关键区域的周围洁净环境一般是 ISO7.在合适的风险管理控制下，使用隔离器可以降低周围环境标准；很多新的生产设施使用 ISO8 作为背景环境依照 2004FDA 无菌工艺指南或欧洲 GMP 附录 1（2）。

Open isolators are typically installed in ISO 8 **(Table** 3**.0-1)** environments in order to maintain ISO 5 conditions for material transfers and operations. The surrounding clean area is where the personnel performing the manual processes are located. Appropriate gowning facilities are required which are consistent with the background environment requirements. The execution of the MAP is ordinarily supported by various sterilization processes for the materials and equipment required, and these sterilization processes may also be located in the support areas.
开放式隔离器一般安装在 ISO8 环境中以为物料传递和操作提供 ISO5 环境。人员进行人工操作的洁净区域的位置是固定的。合适的更衣设施需要与背景环境要求一致。MAP 的执行通常也要通过对需要的物料和设备的各种灭菌工艺来支持，并且这些工艺也应设置在支持区域。

The overall flow of the MAP facility, personnel and equipment is consistent with large-scale environments utilized for equipment-based aseptic filling, whether in a cleanroom or an isolator, but on a much smaller scale.
MAP 设施、人员和设备流向应与自动无菌灌装使用的大范围的环境一致，无论是洁净室或者隔离室，还是更小的区域。

4.0 Operational Personnel Training and Qualification
操作人员培训和确认

People are the most critical operational variable and represent the highest source of contamination in manual aseptic processing. Operational personnel must be highly proficient at their assigned tasks. Therefore, personnel training and qualification become critical to success
人员是最重要的操作变量，也代表无菌操作过程的最大污染源。操作人员必须熟练自己的操作。因此，操作人员培训和确认是很重要的。

4.1 Personnel Training and Qualification
人员培训和确认

The training requirements for operational personnel typically include the usual elements of cGMP:
操作人员的培训要求包括 CGMP 的这些常见元素：
• Microbiological principles 微生物原则；
• Sterility assurance 无菌保证；
• Gowning practices 更衣操作；
• Good aseptic practices 良好的无菌行为规范；
•灭菌。

Theoretical knowledge of these disciplines alone is insufficient. Operators must be able to adapt the classroom learning to the real world manufacturing environment. Operators must excel in the execution of those tasks that directly impact sterility assurance: aseptic gowning, aseptic assembly and aseptic technique. They must be able to consistently perform precision tasks without introducing contamination to the materials with which they are working.
单纯的理论知识是不够的。操作人员一定要将课堂知识应用到实际中去。操作者一定要合格执行这些直接影响无菌保证的操作：无菌更衣，无菌组装和无菌技术。他们一定要能够持续的完成精细的工作而不对物料引入污染。操作人员完成初始更衣资格确认后，它就可以进入无菌核心进行持续的无菌工艺指导。

4.2 Gowning Qualification
更衣确认

Assessment of the operators' proficiency in their assigned tasks can be established through practical exercises in which their skills are challenged and evaluated. The most basic of these tasks, and one of the first at which the operator must succeed, is aseptic gowning. This involves repetitive gowning in full aseptic garb under the observation of a fully qualified individual followed by monitoring of gown surfaces. The number of monitored gown surfaces varies with the company, but typically includes: gloves, forearms, and chest area, i.e., the body locations closest to any manual aseptic manipulations the operator must perform ***(6).*** The operator must successfully demonstrate his/her ability to meet the defined monitoring levels after each gowning exercise. Gowning certifications should be conducted on a periodic basis to confirm that the operators maintain consistent gowning practices. Once the operators have passed initial gowning certification he/she is granted access to the aseptic core for the continued instruction in aseptic processing.
对操作人员完成工作能力的考核可以通过实际操作进行，在实际操作中他们的技能可以被考核和评

估。这些操作中最基本的也是一个首要掌握的就是无菌更衣。这包括在一个完全合格的人员的观察下重复穿无菌洁净服，然后检测衣服表面。检测的无菌服表面数量因公司而异，但一般包括：手套，前臂，胸口，例如人体距离操作人员进行无菌操作距离最近的位置。操作人员必须证明更衣后他能满足监测标准。更衣资格必须定期确认以确认操作人员一直能够良好更衣。

Note: The need for operator gowning qualification is based on the nature of the isolator process and should be evaluated by a risk assessment.
备注：更衣确认的需求是基于隔离工艺的特征，并要通过风险评估来评价。

Following a long term absence, adverse trend or out of limits in gowning results (and based on investigation) operators should be requalified for gowning.
长时间不在岗位、不良趋势或更衣结果超标（并在调查的基础上）操作人员应重新进行更衣确认。

4.3 Risk Management
风险管理

The approach of Quality Risk Management (see also PDA Technical Report No. 54 *(11)* and its annex documents with case studies) is highly recommended for manual aseptic processes. As stated in PDA Technical Report No. 44:
风险管理的方法强烈推荐应用与人工无菌操作（间 TR54（11）和带案例分析的附录）。如 TR44 所述：

> *Process failures that can result in elevated endotoxin levels and lack of sterility assurance pose a significant risk to patient safety. The ability to detect a process failure is low given the current methods for sterility testing The probability of a process failure that could adversely affect the sterility of the product in aseptic processing is higher and less predictable than in terminal sterilization, given the inherent exposure to environmental contaminants. Quality risk management can be an effective method of identifying and reducing aseptic processing risk, thus improving the assurance of sterility, endotoxin control, and subsequent patient safety (12).*
> *工艺失败可能导致内毒素升高，缺少无菌保证可能给病人带来很大风险。在现有的无菌测试方法下，检验工艺失败的能力是低的。由于暴露在环境污染物中，无菌工艺中可能影响产品无菌性的工艺失败的可能性很高，比最终灭菌产品更难预测。质量风险管理可以成为一个辨别并减少无菌工艺风险的有效方法，因而提高无菌保证，内毒素控制和病人安全。*

Manual aseptic processing involves greater risks than automated aseptic processes. A risk-based quality management approach can be very helpful. It is therefore essential that there is a thorough and complete understanding of the process, including critical steps and risks, so that any risk assessment is appropriately informed.
人工无菌工艺比自动无菌工艺风险更大。基于风险的质量管理方法很有帮助。因此对于工艺彻底完全的理解，包括关键步骤和风险，这很重要，从而风险评估可以合理进行。

4.4 Aseptic Handling Challenges 无菌操作考核

The conventional means for establishing personnel proficiency in aseptic processing is through participation in an APS, (also known as a media fill) (1, 6). The APS requires the operators to perform aseptic interventions during the normal course of the simulation that are typically conducted during

manufacturing. Those charged with aseptic assembly will assemble the sterilized equipment prior to the media fill. These activities are important for several reasons:
确定人员无菌工艺操作能力的常用方法是通过参与 APS（也成为培养基模拟灌装）。APS 要求操作人员在正常模拟程序中进行一些生产过程中遇到的无菌干扰行为。那些负责无菌组装的将在培养及模拟之前进行已灭菌器具的组装。因为如下原因这些行为很重要：

- MAP is more susceptible to human contamination than automated aseptic processing
  MAP 比自动无菌工艺更容易引起人员污染；

- Interventions on manual aseptic systems are frequent and may be complicated by suboptimal equipment design
  人工无菌系统干扰时拼房的，并且由于设备设计不佳可能变得更复杂。

Thus, an individual who has demonstrated proficiency at large-scale industrial aseptic processing must still demonstrate his/her proficiency in the more rigorous requirements of MAP. This is often accomplished by various challenge tests in which the operator must directly handle sterile equipment and materials (usually with media) to demonstrate his/her aseptic technique. These tasks should be representative of the actual process steps. The operators are required to demonstrate aseptic practice proficiency in these evaluations regardless of the technology utilized.
因此一个证明能够进行大规模工业无菌工艺操作的人员仍然需要证明其在更严格要求的 MAP 中操作的能力。这通常是通过许多测试完成，在这些测试中人员直接接触无菌设备和物料（通常有培养基）来证明它的技术。这些操作要能代表实际的工艺步骤。不管应用什么技术，操作人员都要在这些考核中证实其无菌操作能力。

5.0 Equipment Components and Container/Closure
设备，成分和容器/密封件

The equipment, raw material components, containers, closures and other items required for MAP vary with the requirements of the process. These items are typically reduced in size or quantity, which allows so they can be supplied to the processing environment in a sealed package after depyrogenation/sterilization. The preparation methods for such sealed packages prior to depyrogenation/sterilization are similar to those associated with automated aseptic processing though on a smaller scale of operation. The depyrogenation/sterilization methods for all of these items are required to be validated. When sterile containers/closures are purchased from a commercial source, procedures should be in place and implemented to ensure the sterility of these items are maintained when introduced into an aseptic environment and used in production. Where sterilization or depyrogenation of processes for non-product contact surfaces cannot be utilized, a validated sanitization process is required to be performed.
要求 MAP 的设备、原辅料、容器、盖子和其它项目根据工艺要求而不同。这些项目都减少了尺寸或数量，这样就可以在灭菌后装入密封包装然后转运到生产环境中。尽管操作量更小，但是对于此类密封包装的提前除热源/灭菌的操作方法与无菌操作工艺类似。除热源/灭菌的方法都应经过验证。当从外部购买无菌容器、盖子的时候，当要转入无菌环境用于生产时，要在公司进行一些程序来确保这些物料的无菌。不接触无聊的表面无法进行除热源或灭菌时，要用采经验证的消毒工艺。

6.0 Process Time Limitations

工艺时间限制

Personnel time limitations with MAP are usually more important than with automated aseptic processes. In very short or nonrepetitive processes, such as an aseptic connection, time may be of little relevance (except as it may relate to material stability) and its impact lessened. Where operators must perform repetitive tasks such as container filling/stoppering, egg harvesting (as in vaccine manufacturing) or similar tasks, the effect of fatigue must be considered in both routine operation and process simulation. The operator's aseptic technique may deteriorate with the passage of time. A "worstcase" evaluation of fatigue would include a process simulation equal or greater in time duration to the longest period an operator might perform the task without interruption. Similarly, a process simulation conducted at the end of a normal day's production can evaluate the effect of fatigue on the operator's aseptic technique (1,5,6,13).

MAP 过程的人员操作时限通常比自动无菌工艺过程更重要。在很短的或不可重复的操作过程中，像无菌连接，时间可能关系不大，影响减弱（除非影响到材料稳定性）。对于操作者必须进行重复操作的工作，例如容器罐装/加塞，病毒收获（在疫苗生产时）或相似的任务，疲劳的影响一定要在常规操作和工艺模拟中考虑。操作者的无菌操作可能随着时间延长而变坏。关于疲惫的最差条件的评价要包括要进行工艺模拟等于或大于操作人员不间断工作时的最长时间。类似的，在一个正常工作日后进行工艺模拟可以评价疲劳对于操作者无菌操作技术的影响。

Time limits for holding dirty/clean/sterile equipment and sterile/depyrogenated components shall also be validated. It is also necessary to validate the maximum time allowed between formulation (addition of the first ingredient, which includes water) to the point of sterilization (filtration considering filter grow-through) and the validation of holding sterile bulk through usage. These topics are discussed in PDA Technical Report No. 22 ***(6)*.**

存放非洁净的/洁净的/无菌的设备和无菌的/去热源的成分的时限应该被验证。也需要验证药液到灭菌前的储存时限以及无菌中间体的保存时限。这些在 PDA TR22 中讨论。

Note: As part of the process risk assessment, personnel fatigue factors need to be considered, and where possible minimized/eliminated through improvement in ergonomics, an understanding of human factors, etc.

提示：作为工艺风险评估的一部分，人员疲惫因素需要被考虑，并且要通过提高人类环境学内容、理解人员因素来尽可能减少风险。

7.0 Design of Manual Aseptic Processes
手动无菌操作的设计

Sterility assurance requires a holistic approach to the entire manufacturing process, and encompasses appropriate facility/equipment/process design, aseptic practice/validation and a well thought out risk assessment to mitigate contamination. Considering the importance of personnel practices in MAP, the process should be designed to minimize the impact of personnel. General process design principles that will reduce the risk of contamination are outlined below.
无菌保证要求对整个生产工艺有一个整体的方法，并包括适合的厂房设备和工艺审计，无菌行为/验证和考虑周密的风险评估来减少风险。考虑到人员行为的重要性，工艺应设计为了减少人员影响。减少污染的设计原则如下。

7.1 Manual Aseptic Process Design Principles in Unidirectional Air Flow Hoods
在无方向性的层流罩下的手动无菌操作设计

The list below elaborates on design principles for manual aseptic processing.
以下详细列出了关于手动无菌操作的设计原则

- Adequate space to perform the work.
  完成工作足够的空间
- All exposed product and product-contacting components should continuously remain in First Air, i.e., the work location first in the path of HEPA-filtered air.
  所有暴露的产品和与产品直接接触的部件应始终位于未经过其它物体的气流下，如工作点应该在经高效过滤的空气流动路径的开始处。
- Aseptic manipulations should be made in First Air, not having passed over any other components or blocked by the operator's hands.
  无菌操作应在初始气流下完成，不能经过其它部件或者被操作者的手部阻挡。
- The operators should decontaminate or change their gloves on a frequent basis.
  操作者要以一定的频率对手套灭菌或者更换手套。
- The operators should work as a team. The primary operator(s) should perform all tasks inside the ISO 5 environment. The secondary operator(s) assists in the introduction/removal of items from the ISO 5 environment, and may assist the primary operator(s) with less critical tasks inside that environment. Additional support operator(s) may be necessary to support activities exclusively in the surrounding environment.
  操作者应成组工作。主要操作者应在 ISO5 环境下完成所有工作。次要工作者应协助传入或传出 ISO5 环境下的物料，并帮助 ISO5 环境中的完成低风险的工作。其它支持人员只在周围环境提供支持活动。
- The primary operator should wear sterile gloves and sleeves and never contact a non-sanitized or non-sterilized item.
  主要操作者应该穿着无菌手套和套袖并且不能接触非消毒或非无菌物料。
- The primary operator(s) performs the critical aseptic manipulations within the ISO 5 environment. The secondary operator(s) acts as a support person to minimize the potential of the primary operator touching non-sterile or non-disinfected surfaces. The hands of the primary operator should remain in the ISO 5 environment at all times. (There may be exceptions to this related to positron emission tomography products or radioactive products.) The secondary operator(s) should put on sterile

gloves/sleeves prior to any activity inside the ISO 5 environment, or in transfers of items t o / from the primary operator. Anytime the primary operator is required to leave the ISO 5 environment, gloves and sleeves (if appropriate) should either be changed or gloves should be re-sanitized prior to reentry to ISO5.

- 主要操作者在 ISO5 环境中从事关键无菌操作。次要操作者作为协助人员目的减少主要操作者接触非无菌或未灭菌表面的可能性。主操者的手要一直放在 ISO5 环境中。（对于正电子成像或者放射性药品可能有例外）次要操作者应该在进行 ISO5 环境下操作之前想穿上无菌手套或者套袖，或者通过传递窗递给或取出。在任何时候，主要操作人员离开 ISO5 环境下，再次进入时都需要更换手套套袖或者重新消毒。
- Sterilized items should be introduced to the ISO 5 area by aseptic removal of the final wrap around the item as it is being introduced.
  灭菌物料引入无菌区时要通过无菌去除物料外围的包装。
- Extra subassemblies and utensils should be sterilized and available for immediate use in the event a replacement is needed.
  额外的组件或工具应该灭菌，并且要在需要替换的时候随时可用。
- Sterile tools and utensils should be employed wherever possible *to handle sterile materials during their processing*, rather than the direct contact with the operator gloves. There should be sterile supports or hangers for tools inside the ISO 5 environment in order to minimize contact between the tool and surfaces of the workspace.
  工艺过程中传递无菌物料时应该使用无菌工器具，而不是直接用手套接触。应该在无菌区设置无菌支架或挂架来减少工具与工作场所表面的接触。
- The process should be designed so that samples can be taken with minimal risk of contamination. When withdrawing samples f r om a sterile container, it is preferable to take all desired samples from a container in a single step, and then subdivide that sample as required. Alternatively the residual left in the original container post-production can be used as the test sample. The use of technologies such as sterile septum or connectors should be considered to minimize the risk during sampling.
  工艺设计应注意减少取样引入风险。当样品从无菌容器中取出时，最好一次取出所有希望的样品，然后按要求分样。另外，生产结束后原容器中残留的样品可以用做测试样品。无菌隔膜或连接器这类技术应考虑用于减低取样风险。
- Wherever possible materials being introduced into the process should be pre-measured into a tightly sealed container prior to sterilization and addition.
  但凡可能进入无菌区的物料应预先盛装在完全密封的容器中进行灭菌。
- Electrical equipment and controls pose a contamination risk and should be located outside the processing environment, if possible. If that is not possible a second operator (not the primary operator) should adjust equipment settings as necessary. Pay special attention to equipment which exhausts air (e.g., mixers, blenders, etc.) that could contaminate the environment.
  电器和控制装置可能引入污染的风险，如可能，应当放置于无菌生产环境之外。如不可行，那么应有次要操作者（不是主要操作者）用来调节仪器的设置。对于会排放气体的仪器（例如：混合器、搅拌器等）要特别注意，因为它们可能污染环境。
- Liquid transfers should be made using peristaltic pumps located outside the aseptic environment, rather than through the use of automatic pipettes, due to concerns regarding exhausted air. In order to minimize equipment movement and the risk of contamination, containers can be premarked to indicate the amount of material to transfer.
  液体转移应使用置于无菌区外的蠕动泵，而不是使用自动移液器，这是基于对排出气体的考虑。

为了使仪器的移动和污染的风险降到最低，用于转移的容器可以根据需转移物料的数量体积提前做好标志。

- Perform as much of the process inside the ISO 5 environment as possible in order to minimize the removal and reentry of in-process materials in suitable containers. This may require the placement of small equipment within the environment.
  要最大限度符合 ISO5 环境级别的操作以使中间过程物料在合适的容器中的传出和传入降至最低。这可能需要在环境中放置小型仪器。
- When containers of in-process materials must be removed from, and later returned to, the ISO 5 environment the containers should be aseptically wrapped in a pre-sterilized covering which should be properly removed and discarded prior to reentry. Alternatively, the exterior of the container(s) can be re-sanitized prior to reentry.
  当放置中间物料的容器需要从 ISO5 环境中传出，并且稍后再传入，该容器需用预先灭菌并且在再次传入前易于移除的无菌材料包裹。或者，最外面一层容器在再次传入前再次消毒。
- Sanitize the operating environment when it is empty, and sanitize each nonsterilizable item/equipment as it is first introduced and transferred into the next cleaner level of the aseptic processing environments. Do not introduce a large item into the environment in mid-process. Note: If sanitization of the operating environment/ equipment is performed by the primary operator, sterile gloves/sleeves should be changed before aseptic manipulation of product is performed.
  非生产期间对操作环境进行消毒，对要传入邻近无菌操作环境中的非灭菌器具、仪器，在首次传入之前要消毒。在生产过程中不能向环境中引入大型器具。注意：如操作环境/仪器的消毒是由主操完成的，在无菌生产操作前要更换无菌手套。
- Product contact surfaces shall be sterilized. Sterility should be maintained with protective layers which can be removed as materials are transitioned to cleaner environments.
  产品可接触到的表面应灭菌。当物料需转移至无菌区时，应由保护层来保证无菌性。
- Significant aseptic assembly in the processing environment should be avoided through the use of sterilized pre-assembled items. This will reduce the extent of manual assembly required.
  器具灭菌前进行预组装，避免在 ISO 5 环境做主要的无菌组装。这将减少手工组装的需要。
- Process steps not required to be aseptic should be performed outside the ISO 5 environment by other operator(s).
  非无菌工艺步骤应由其他操作人员在 ISO5 级别环境之外完成。

- Once the process design has been established, it should be rehearsed several times and documented in air flow studies using all of the required items and placebo materials to refine the steps, location of items, etc. This ensures the process design is practical and reduces risk of contamination to a minimum. The use of engineering runs to develop the process is strongly encouraged.
  一旦建立了工艺方案，应使用所需器具和安慰剂对每一工艺步骤重复进行并记录空气流型研究，以改善每一步骤和器具的摆放位置等。这将保证工艺的可行性，并将污染的风险降低至最低。我们强烈鼓励使用工业设备提高工艺。
- The manufacturing process should be documented in sufficient detail to allow operators to understand and conform to the desired practices. The secondary or support operator(s) should complete the batch record.
  生产过程的记录应记录足够详细使操作人员能够理解并且符合预期操作。批记录应由另一名操作员应完成。
- Environmental monitoring practices should be non-intrusive in order to avoid potential for

contamination in the ISO 5 environment. Air sampling during processing may be performed with specially designed equipment that does not compromise the environment and may include settling plates. Surface monitoring should be performed using contact plates or swabs after processing has been completed.
为了避免对 ISO5 级别环境的潜在污染，环境监测应采用“非侵入式”。生产过程中空气采样应使用特殊设计的不破坏环境的设备，可能还包括沉降碟。表面微生物监测应在生产结束后使用接触碟或棉签。

7.2 Manual Aseptic Process Design Principles in Isolators and RABS
手动无菌工艺中隔离器和 RABS 的设计原则

The use of an isolator for manual aseptic processing requires some adaptation to the methods described above. Isolator characteristics include the following:
使用隔离器进行手动无菌操作需要对上述方法做出一些改变。隔离器操作的独特性如下：

An isolator is scaled or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may he reproducihly decontaminated. When closed it uses only decontaminated (where necessary) interfaces or Rapid Transfer Ports (RTFs) for materials transfer. When open it allows for the ingress and/or egress of materials through defined openings ("mouse holes") that have been designed and validated to preclude the transfer of contamination. Isolators can be used for aseptic processing activities, containment of potent compounds, or simultaneously for both asepsis and containment (14).
隔离器是指一个封闭的系统或者通过过滤器（至少为高效过滤器）提供洁净空气的系统，甚至可以实现在线消毒。当隔离器关闭时，仅使用消毒的接口或者快速转移接口（RPTs）进行物料传递。当隔离器打开时，可以通过经验证的开口（鼠洞）传入或取出物料，该开口的设计旨在消除物料传递带来的污染。隔离器可以用于无菌工艺生产，隔离有活性的化合物，或者同时用于两者。

Restricted access barrier systems (RABS) vary with respect to their design. Where items are introduced using a rapid transfer port (RTP) their use resembles that of isolators described below. RABS lacking these features may have greater resemblance to manned clean rooms and their design and operation is more like that described above for Unidirectional Air Flow Hoods.
RABS 根据设计用很多变化。使用快速转移接口（RPTs）引入物品的方法与隔离器类似。缺失部分功能使 RABS 更像人工洁净室，其设计和操作更像上述的层流罩。

Regardless of the type of isolator or RABS system employed, it should be recognized that these are aseptic, not sterile, process enclosures. Therefore good aseptic technique must be used at all aseptic steps of the process. First air principles should be adhered to where unidirectional flow is provided. In the absence of unidirectional flow, aseptic technique must still be followed consistent with the design of the system (enclosure).
无论使用哪种类型的隔离器或 RABS,我们必须明确，这些箱体，只是经过消毒的，而非灭菌的。因此，先进的无菌技术应伴随工艺中的所有无菌步骤。当提供单向流的时候，最初气体原则也要遵循。在没有单向气流时，无菌技术必须依然遵循密闭系统的设计。

- The enclosure should be decontaminated according to a validated procedure.
  箱体应该按照验证的程序消毒。

- The operators should wear fresh sterile gloves prior to entering the enclosure gloves.
  操作人在使用手套箱前应佩戴新的已灭菌的手套。
- Sterile tools and utensils shall be employed rather than the direct contact with the enclosure gloves. There should be sterile supports for tools and gloves inside the enclosure in order to minimize contact between the tool and horizontal surfaces of the workspace.
  应使用灭菌的工器具，避免裸手接触手套箱，。为了尽量减少工具和工作区表面的接触，箱体内应有支架。
- All items and equipment should be introduced into the enclosure using validated decontamination/ sterilization methods and/or RTPs.
  所有传入箱内的物品和仪器都要使用验证过的消毒/灭菌方法和 RTP 口
- It is preferable to perform as much of the process as possible inside the enclosure to minimize the removal and subsequent reentry of sterile items to the enclosure. This may require the placement of small equipment within the enclosure. When containers of in-process materials must be removed from, and later returned to the ISO 5 environment, the containers should be reintroduced using validated decontamination/sterilization methods and/or RTPs. Alternatively the container can be aseptically wrapped in a pre-sterilized covering (e.g., scalable containers or packages) which should be properly removed and discarded prior to reentry.
  最好在箱体内完成更多的操作，以最大限度减少器具的移除和再次灭菌传入。这可能需要将小型的仪器防止在箱体内。对于中间体容器，需要被传出，随后又要再次传入 ISO 5 级别的环境，该容器的传递需要使用验证过的消毒/灭菌方法和接口。或者将容器用已灭菌的材料（例如：密封的容器或包装袋）包裹，再次传入前彻底去除包裹。
- All exposed product and product-contacting components should always remain in First Air (if present). Aseptic manipulations should be made in First Air from the HEPA filters, not having passed over any other components or blocked by the enclosure gloves. Good aseptic technique must still be adhered to at all times.
  所有暴露的产品或与产品接触的组件都应存放在初始洁净空气中（如果有）。无菌操作应该在经过高效过滤器的初始洁净空气中进行，不得越过任何组件或被手套箱阻拦。必须始终坚持先进的无菌技术。
- Significant aseptic assembly in the ISO 5 environment should be avoided through the use of sterilized pre-assembled items. This will reduce the extent of manual assembly required.
  器具灭菌前进行预组装，避免在 ISO 5 环境做主要的无菌组装。这将减少手工组装的需要。
- Extra subassemblies and utensils should be sterilized and available for immediate use in the event a replacement is needed.
  灭菌备用的组件和器具，在意外发生时立即替换。
- Electrical equipment and controls pose a contamination risk and should be located outside the processing enclosure if possible. If that is not possible a second operator (not the primary operator) should adjust equipment settings as necessary. Pay special attention to equipment which exhausts air (e.g., mixers, blenders, etc.) that could contaminate the environment.
  电力设备和控制装置可能引入污染的风险，如可能，应当放置于无菌生产环境之外。如不可行，那么应有次要操作者（不是主操者）进行仪器调整。对于会排放气体的仪器（例如：混合器、搅拌器等）要特别注意，因为它们可能污染环境。
- Utilize secondary and support operator(s) to supply/remove items to/from the enclosed environment. Wherever possible materials being introduced into the process should be pre-measured into a tightly sealed container prior to sterilization and addition into the barrier.

由副操作员向封闭的环境中传入或移出物品。但凡可能进入无菌区的物料应预先盛装在完全密封的容器中进行灭菌。

- Liquid transfers should be made using peristaltic pumps outside the enclosure rather than through the use of automatic pipettes (due to concerns regarding exhausted air).
  液体的转移应使用置于箱体外的蠕动泵，而不是自动移液器（基于对排出气体的考虑）。
- The process should be designed so that samples can be taken with minimal risk of contamination. When withdrawing samples from a sterile container, it is preferable to take all samples from the container in a single step, and then subdivide that sample as required in another appropriate location. Alternatively, the residual left in the original container post-production can be used as the test sample.
  工艺的设计应将样品取出时污染的风险降至最低。最好一次将样品全部从容器中取出，然后在合适的位置根据需要细分。或者，生产后原容器中剩余部分可用作测试样品。
- Once the process design has been established, it should be rehearsed several times using all of the required items and placebo materials to refine the steps, location of items, etc. The use of engineering runs to develop the process is strongly recommended.
  一旦建立了工艺方案，应使用所有器具和安慰剂重复进行工艺，以改善每一步骤，确定器具的位置，等。我们强烈推荐使用工业设备提高生产工艺。
- The manufacturing process should be documented in sufficient detail to allow the operators to understand and conform to the desired practices.
  生产过程的记录应记录足够详细使操作人员能够理解并且符合预期操作。
- Environmental monitoring practices should be non-intrusive in order to avoid potential for contamination in the enclosure. Air sampling during processing may be performed with specially designed equipment that does not compromise the environment and may include settling plates. Surface monitoring should be performed using contact plates or swabs after processing has been completed.
  为了避免对箱体潜在的污染，环境监测应采用“非侵入式”。生产过程中空气采样应使用特殊设计的不破坏环境的设备，尽量包括沉降碟。表面微生物监测应在生产结束后使用接触碟或棉签。

8.0 Evaluation of Manual Aseptic Processing-Process Simulation
人工无菌操作工艺的评估-工艺模拟

The following are the elements of a MAP simulation that involve extensive participation of personnel in the aseptic process. Details of study design provided in the APS reports on aseptic processing for either filling or sterile bulk production should be consulted for those activities that are essentially unchanged when manual procedures are employed (15).
下文描述的是 MAP 模拟的要素，包括在无菌工艺过程中人员的广泛参与。当应用人工程序时，那些不会变化的行为可以参考关于灌装或者无菌原料生产的无菌过程的模拟报告中提到的研究设计的细节内容。

8.1 Simulation Design
模拟设计

The development of a supporting rationale for the design of the manual aseptic process simulation is essential. The rationale must define the adaptations to the production process necessary for the execution of the simulation. The smaller scale of the manual process lends itself to these adaptations and in many instances only minimal changes to the process are required. In the event of a failure investigation, maintaining the sequence in which samples were filled during the APS can be beneficial in determining at what point contamination was introduced. Definition of these sample points should be included in the rationale. The simulation rationale should be kept current with changes to process, products, components, or equipment that could impact the acceptability of the process.
支持人工无菌操作模拟的设计方案的理论依据的不断发展是很重要的。要为执行模拟需要进行生产工艺的改变必须说明这些改变是合理的。这些改变有时是增加一些小规模的人工操作，许多情况下要求对工艺进行尽量小的改变。做失败调查时，保证模拟灌装时的顺序有利于确定何时引入了污染。模拟的合理性要与工艺、产品、组分或设备这类能够影响工艺的可接受性的变更相一致。
人工无菌操作包括许多活动，可以分为四大类。每类的评估以不同形式进行描述。

Manual aseptic processing can encompass a variety of activities which can be divided into 4 major categories. The evaluation of each category is addressed in a different manner.
人工无菌操作包括许多活动，可以分为四大类。每类的评估以不同形式进行描述。

8.1.1 Compositing/Assembly Activities
合成/组装行为

Compositing/assembly activities involve repetitive actions in which sterile materials in smaller amounts are pooled. Such practices are common in vaccine manufacturing in which the contents of incubated eggs are composited early in the formulation process. Evaluation: For this category, adaptation of the validation methods for sterile filling and bulk materials may be appropriate for the simulation rationale.
合成/组装行为包括小批量无菌材料共用的重复行为。这类的行为在疫苗生产过程中常见。评估：对于这类行为，对无菌灌装和无菌材料采用验证的方法作为模拟的理由是合适的。

8.1.2 Formulation/Compounding Activities
配方/配制行为

Formulation /compounding activities in a manual setting might use different equipment than automated processes due to the smaller scale of the operation. For example, laboratory glassware and utensils may be

used to produce a sterile bulk formulation. The smaller scale of the operation may also mandate alternative transfer methods than those utilized in larger, automated operations. **Evaluation:** The methods utilized for sterile bulk materials may be appropriate in these processes *(1,4, 15)*.
由于小规模操作，人工进行配制比自动过程可能要用到不同的设备。比如，再生产一种无菌配方时可能用到实验室玻璃仪器和器具。小规模生产操作时，可能也要求不同于大规模自动化生产的转移方法。评估：无菌物料采用的方法可能在适合这些过程（1,4,15）。

8.1.3 Filling/Subdivision Activities (Including Lyophilization if Needed)
灌装分装行为（包括冻干,如需要）

Filling/subdivision activities involve repetitive actions in which sterile materials are transferred from a bulk container into smaller containers, sealed and closed (or partially closed when lyophilization is planned). This practice is common in early development and early clinical stage manufacturing of sterile products, and in the manufacture of extremely small lot sizes. Evaluation: These activities may use methods defined for automated filling *(1,6)*.
灌装/分装行为包括重复的动作将无菌物料从大容器中转到较小的容器、密封、盖盖（或者计划冻干时部分盖盖）。这类行为在无菌产品的早期开发、早期用于临床阶段生产、很小批量生产时常见。评估：这类行为可以用确定的方法进行自动灌装（1，6）。

8.1.4 Manual Manipulation Steps Performed in Conjunction with Other Processes
与其它工序结合的其它手工操作行为

Evaluation: Manual activities, such as sampling, aseptic connection, etc., are usually an integral part of other aseptic processes. As such there is no need to address them independently in the rationale for the study design.
评估：手工行为，例如取样、无菌连接等，通常是无菌工艺的一部分。因此没有必要单独说明进行研究设计的理由。关于

Additional details on process-specific evaluation methods are to be provided in conjunction with each of the elements addressed within the overall process evaluation protocol/procedure.
特别工艺的评价方法的详细内容将结合总体的工艺评价方案/程序中的要说明的每个元素一起提出。

8.2 Media Sterilization
培养基灭菌

The preparation of media for use in a MAP simulation is normally managed with few problems. If the media bulk container is small enough it can be sterilized in an autoclave prior to introduction into the process. In other cases non-sterile bulk media may be filtered into the process in a manner similar to the d r u g product. Where possible, sterilization methods, such as autoclaving or irradiating, should be combined with filtration to remove mycoplasma contamination from media components (for a more detailed discussion, see PDA Technical Report No. 22). For compositing/assembly processes, suitable sterile materials to use in the process simulation may be unavailable. In such cases the choice may be to use the production materials themselves suitably sterilized/adapted (if possible and necessary) in the simulation, if they do not inhibit the growth of microorganisms. For the APS each of the liquid containers containing sterile materials for the process should have their contents replaced with media.
用于 MAP 模拟的培养基的制备过程的正常管理过程有几个问题。如果装培养基的容器小到能够在

灭菌柜中灭菌那么就在使用前进行灭菌。否则，非无菌的培养基要像药品那样过滤后使用。如果可能，要结合使用灭菌方法，例如自动灭菌柜或辐照灭菌，以去除衣原体（了解更详细的讨论，见 TR22）。对于合成或组装过程，在工艺模拟过程中可能无法使用无菌物料。这种情况下，可用选择生产用的适于灭菌/使用（如果可能且必要）的物料，如果他们不会阻止微生物生长。对于 APS，每个存放无菌物料的液体容器都要换装上培养基。

8.3 Frequency and Number of APS Runs
APS 模拟的频率和次数

The recommendation for frequency and number of simulation studies (runs) for manual processing is that each operator (primary and secondary) should be qualified semi-annually (or in accordance with the applicable regulatory requirements). Typically, three replicate APS studies are performed to initially qualify an operator and process. The combined duration and size of the APS runs will support both operator and process qualification.

推荐 APS 模拟的频率和数量是每个操作人员（主要操作和次要操作）每半年确认合格（或与适用的法规一致）。通常，要进行三次重复的 APS 来做人员和工艺的首次确认。APS 过程中批量和模拟时间的结合也能支持人员和工艺的确认。

Note: Operator qualification is critical since the operators are the primary means of production. More frequent studies may be required for infrequent manufacturing operations.

备注：人员确认是重要的因为人员是主要的生产途径。对于少见的生产操作可能要求更频繁的研究。

8.3.1 Duration of Runs
模拟时间长度

Simulation studies should meet or exceed t h e expected maximum duration of a single working session by a single operator.

模拟研究要满足或者超过单个操作人员单个工作程度可能进行的最长的时间。

8.3.2 Size of Runs
模拟的批量

The size of the process simulation is largely dictated by the time period that a single operator would remain performing the same activity. The actual numbers of units produced in that time period should meet or exceed the production quantity that the operator(s) would normally handle in that time period. As t h e operator is an integral part of the process and a key variable in MAP, it may be that each operator will have to perform the whole process simulation for t h e process to be considered valid especially where only small numbers are filled.

工艺模拟的批量主要取决于单人持续同一操作的时间段。那个时间段产出的实际的数量应满足或超过那个时间段正常生产出的产品的数量。由于操作者是工艺的一部分而且在 MAP 中是一个关键变量，可能需要 每个操作者完成工艺的整个模拟过程才是有效的，尤其是只灌装少量的时候。

8.4 Observation of the Process Simulation
工艺模拟过程的观察

Considerations for observation of MAP simulations are consistent with observations of automated simulations, as described in PDA Technical Report No. 22 *(6):*

MAP 模拟过程中观察要与自动模拟过程中的观察一致，如 TR22 中所述：

The process simulation should he observed to assure that all planned activities are properly executed and represent an appropriate challenge to the process capability Observation may also be used to augment aseptic conduct and technique training.
要观察工艺模拟过程以保证所有计划的行为都被合适的执行，并且合适的挑战了工艺。观察也用于加强无菌操作和技术培训。

Observation should commence upon the initiation of the process simulation, including equipment set-up, and continue until the process simulation has completed. Observation of the simulation should be performed by individuals having the knowledge and competency to assess if operators have used proper aseptic conduct in their activities. These individuals should also b e able to assess that aseptic interventions have been executed consistent with good practice so as to provide for realistic assessments of sterility control.
观察需要从工艺模拟启动就开始，包括设备组装，进行到工艺模拟完成。模拟的观察需要由有知识和能力的人来进行以评估操作者是否用了无菌操作行为。这些观察人员还要能评估无菌干扰是否按照规定正确执行以真实评估无菌控制。

The process simulation observation should be documented and/or video recorded. The use of video recording of the APS allows activities to be reviewed in detail to assist with training or failure investigation *(6)*.
工艺模拟观察需要文件记录或者摄像。摄像能够审核细节 有助于培训和失败调查。

8.5 Media Fill Volume
培养基模拟灌装体积

In aseptic filling simulations the amount of media transferred during the simulation should be sufficient to wet the product contact surfaces of the container and be sufficient to detect growth. In compositing simulations, the amount of media transferred should be identical to that normally handled in production to simulate the process duration more accurately. In manual manufacturing simulations, the volumes of media and other fluids (which should all be replaced with media) should be identical to, or greater than that in the process to be simulated. The goal is to assure that the sterile product components (e.g., containers, closures, and media) are exposed for the maximum length seen during routine manufacturing, thus assuring the simulation represents a comparable risk as routine processing.
在无菌模拟灌装中，模拟过程中转移的培养基的体积要足够湿润产品接触的容器的内表面，并足够用于检测生长。在合成？模拟过程中，转移的培养基的量应与正常生产过程中处理的量一致以便更好的模拟工艺时间。在人工生产模拟中，培养基或其它液体（都要被培养基替代）应等同于或者比被模拟的产品更大。目的是为了保证无菌部分（如容器、盖子、培养基）暴露了常规生产过程中看到的最长时间，以此保证模拟了与常规工艺生产中可能遇到的相当的风险。

8.6 Anaerobes/Inert Gassing
厌氧菌/惰性气体

The methods utilized for automated, machine-based aseptic processing can be adopted without change. Air should be substituted for inert gases in all systems, except in those rare instances where an isolator providing true anaerobic conditions is utilized for the production process environment. In such situations, the usual inert gas would be utilized and the appropriate media would generally be fluid thioglycollate

media (FTM) or alternative FTM (if filtration of the media is necessary).
用于自动、机械无菌工艺的方法可以不用变化的采用。在所有系统中，可以用空气代替惰性气体，除了很少的情况下有隔离器提供用于生产工艺环境的真的厌氧条件。在这种条件下，可使用通常的惰性气体并且应用 FTM 或者可替代的 FTM（如果培养基过滤是必要的）。

8.7 Environmental Monitoring
环境监测

Environmental monitoring for MAP uses methods generally the same as those for other highly controlled (ISO 5/7) environments. The same cautions exercised with monitoring in other systems apply to MAP as well. Sampling activities must not introduce contamination into the environment or into the sample. Since the environmental systems utilized for MAP are of smaller size, the monitoring methods must be chosen for their lack of impact on the environment. A thorough understanding of the process should be used to ensure that areas of greatest risk are monitored at the appropriate frequency using the appropriate monitor *(1,2,4,6,14)*.
MAP 环境监测用的方法与严格控制的环境 ISO5/7 所用方法一致。其它系统环境监测时注意事项同样适用于 MAP。由于用于 MAP 的环境系统范围较小，监测方法要选择对环境影响小的。对工艺的通透的理解能够药政采用合适的监测器及合适的频率来监测最高风险区域。

8.8 Execution of the Simulation
模拟的执行

The process simulation should be performed in a manner that properly documents the activities. A batch record designed specifically for the simulation should be used. The presence of an observer who documents the simulation is recommended. The methods and principles defined for automated filling or sterile bulk chemical production can be utilized with relatively minor modifications.
工艺的模拟的执行要通过合适的文件记录行为。要用专门设计用于模拟的批记录。推荐由一个观察人来记录模拟。用于自动灌装或无菌化学物生产的方法和原则通过相对小的改动可以应用。

8.9 Pre-Incubation Inspection
培养前观察

The pre-incubation inspection methods utilized for automated, machine-based aseptic processing can be adopted without change. As the containers in MAP are more likely to be hand stoppered and /or sealed, and subject to more variability, pre-incubation inspection must be performed with the same rigor as product inspection. The same caution should be applied to inspection of hand-sealed production units for the same reasons. Units with defective seals should be removed from the materials sent for incubation. Units with cosmetic defects should be treated as integral and included in the incubation.
用于自动、机械无菌生产的培养前检查方法可以不需改变的使用。由于 MAP 过程中的容器更可能手动加塞或密封，变量更多，培养前检查必须按照产品检查一样严格执行。同样原因，同样需要注意手动密封产品的检查。密封缺陷的单元需要送去培养前剔出。表面有问题的单元需要培养。

Note: Generally, the number and type(s) of defective units should not exceed those generated during routine manufacturing.
备注：通常，缺陷单元的数量和类型不得超过平时生产产出的单元。

8.10 Incubation Time/Temperature

培养时间/温度

The same incubation methods used for a u t o m a t e d machine-based aseptic processing are appropriate for MAP and can b e f o u n d in PDA Technical Report No. 22 *(6):*
用于自动机械无菌工艺的培养方法也适用于 MAP，可以查看 TR22：

Prior to incubation, units should be inverted, and swirled or manipulated to ensure contact of the medium with all internal surfaces of the closure system before they are incubated. Process simulation units should be incubated for a minimum of 14 days unless supported by another qualified duration/method. The temperature chosen should be based upon its ability to recover microorganisms normally found environmentally or in the product bioburden. A single incubation temperature in the range of 20-35 ℃ may be used. Data should be available to show the suitability of the selected incubation temperature to support growth. The selected temperature should be controlled and monitored continuously throughout the incubation period.
在培养之前，灌装的单元要倒装、翻转或者其它操作来保证培养基与密封组件整个内表面接触。工艺模拟的培养基至少培养十四天，除非有其它确认过的时间或者方法。温度的选择基于温度要能使环境常规发现的微生物或产品生物负载的微生物能够复活。可以使用 20-35℃范围内的单一培养温度。要有数据说明选择的温度能够支持生长。选择的温度要在培养期间持续控制盒监测。

8.11 Post-Incubation Inspection

培养后检查

The incubation methods utilized for machine-based aseptic processing are appropriate for MAP and can be found in PDA Technical Report No. 22:
用于自动机械无菌工艺的培养方法也适用于 MAP，可以查看 TR22：

At the end of the incubation period, visual inspection of all units for growth is performed to determine the final results of the aseptic process simulation. The inspection process should be performed by trained inspectors who have demonstrated the ability to detect both low and high-level microbial growth patterns. Firms may choose to inspect units partway through the incubation period.
培养结束时，要目测所有的灌装单元的微生物生长情况以确认无菌工艺模拟的最后结果。检查过程需要被培训合格的检查人员完成，他们要能够检查出低程度和高程度的微生物生长模式。在培养期间，公司可以选择中途检查培养基。

As the pre-incubation inspection is expected to remove any units with container/closure defects, if a positive unit is detected during the post-incubation inspection it must be appropriately investigated for cause and corrective action *(6).*
在培养前的检查中，应挑出所有容器/密封件有缺陷的单元，如果培养后的检查过程中，发现有阳性单元，必须进行适宜的调查以确定原因并制定纠正措施(6)。

8.12 Growth Promotion

促生长试验

The methods and considerations relevant to automated machine-based aseptic processing are adopted without change as in PDA Technical Report No. 22 *(6):*
用于自动机械无菌工艺的培养方法也适用于 MAP，可以查看 TR22：

The medium's growth properties should be evaluated using pharmacopeial methods, and the inclusion of environmental organisms or those isolated from sterility test positives may be beneficial. Growth promotion should be performed after 14 days of incubation.
培养基的支持生长的性质要通过使用药典方法和培养环境微生物或从无菌测试阳性菌分离的微生物来进行评价。促生长试验要在培养 14 天后进行。

Suggested pharmacopeial methods include USP <71 > *(1)* and *Ph. Eur.* 2.6.1 *(S)*.
建议的药典方法包括在 USP<71 > (1)和欧洲药典 2.6.1 (S)中。

8.13 Interpretation of Test Results
测试结果的解释

Production lots produced by MAP are typically smaller than the current standard minimum simulation size of 5,000 units. Thus VIAP simulations conducted in support of container filling must have a contamination frequency of zero (0) filled units. In compositing or formulation simulations, the simulated bulk material container(s) should be sterile. Consistent with PDA Technical Report No. 22:
MAP 生产的产品批量一般比现在要求模拟的最小量 5000 单元要小。要支持容器灌装 MAP 模拟必须实现灌装单元 0 污染。在合成或者制剂模拟中，模拟的物料容器应是无菌的。与 TR22 一致：

Regardless of the number of units filled during a process simulation or the number of positives allowed, the ultimate goal for the number of positives in any process simulation should be zero. A sterile product is, after all, one which contains no viable organisms.
不管模拟过程灌装了多少单元，或者允许阳性的数量，在任何工艺模拟中阳性数量的最终目标是 0。一个无菌产品最终是不含任何活的微生物的。

There are, however, numerous technical problems in achieving this goal. Media and simulated product do not match real products perfectly in terms of their processing characteristics and microbiological growth-support properties. Media differ in many respects from the products they are intended to simulate; for example, there are differences in solubility, pH, filtration rates and filterability and viscosity. With powdered products, the process simulation involves reconstituting powdered media or simulated product, introducing extra processing equipment or manipulation, with the inherent risk of contamination. Since a microbiological medium is designed specifically to support or stimulate the growth of microorganisms, it is a more rigorous challenge than processed products, which often provide neutral and sometimes hostile microbial growth environments *(6)*.
然而，要达到这个目标有很多技术问题。由于真实产品的工艺特征、支持微生物生长的特性，培养基和模拟产品不能完全匹配真实生产的产品。培养基在很多方面不同于打算模拟的产品；例如，它们的溶解性，pH，过滤速度和可滤过性和粘度不同。对于粉末产品，工艺模拟包括复原粉末培养基或者模拟产品，

Although Technical Report No. 22 makes provision for some low number other than zero, in the case of manual aseptic processing this criterion must be set to zero due to the manual nature of the operation. The assumptions used for low numerical acceptance are not applicable for manual aseptic processing operations.
引入带有一样风险的额外的设备或操作。由于微生物培养基是专用于支持或者模拟微生物生长的，它比生产的产品是更严格的挑战，生产的产品经常是中性的，有时不是微生物生产的好的环境。尽

管 TR22 规定了非零的小的数量，但对于人工无菌操作，由于手工操作的特性，标准要设定为 0。低数量的接受标准不适用于手工无菌操作。

9.0 Conclusion
总结

This technical report is o n e of the first attempts to address the subject of manual aseptic processing in a comprehensive manner. As such, it includes recommendations that may establish recommended practices in the absence of guidance from regulators or industry organizations. Manufacturers that use manual aseptic processing to produce products used in patients must be aware of the uncertainties associated with a manufacturing process so heavily reliant on personnel performance. In new installations, we strongly encourage the use of isolation technology to minimize the risk of microbial contamination from personnel involved in the manufacturing operations.

这个报告是初步宽泛的介绍了人工无菌操作过程的内容。因而，它包括了一些法规或者行业组织指南中没有的建议可以指导实际工作。采用人工无菌操作的生产企业必须意识到因人工操作带来的不确定性与人员操作紧密相关。建立新设施设备时，我们强烈推荐使用隔离技术来减少生产操作中来自人员的微生物污染的风险。