一次性生物加工系统的辐照灭菌验证指南

Radiation Sterilization Verification Guide for Disposable Bioprocessing Systems

一次性生物过程制造系统越来越多地被通过基于安全、省时和降低成本的好处的生物制药行业得以实现。这些一次性系统用于处理或盛装从培养基、添加剂和缓冲液，到散装半成品和最终制剂的液体。在许多情况下，为确保产品的纯度和安全性，要求控制微生物和无菌。辐射灭菌是适用于一次性使用系统常用的微生物控制和灭菌方法。 在制药行业，验证射线灭菌的标准方法并不广为人知，这个行业历来依赖温湿(蒸汽)对不锈钢生物工艺系统进行灭菌。

Disposable biological process manufacturing systems are increasingly being implemented in the biopharmaceutical industry based on the benefits of safety, time saving and cost reduction. These disposable systems are used to process or contain liquids from culture media, additives and buffers, to bulk semi-finished products and final formulations. In many cases, control of microorganisms and sterility is required to ensure the purity and safety of the product. Radiation sterilization is a common microbiological control and sterilization method suitable for use in disposable systems. In the pharmaceutical industry, the standard method of verifying radiation sterilization is not widely known, and the industry has historically relied on temperature and humidity (steam) to sterilize stainless steel bioprocess systems.

在塑料工业协会的主持下，BPSA 技术委员会成立了一个小组委员会，制定一次性生物过程组件和系统的辐照和灭菌指南。

Under the auspices of the Plastics Industry Association, the BPSA Technical Committee established a subcommittee to develop guidelines for irradiation and sterilization of disposable biological process components and systems.

范围、目的，和背景

Scope, purpose, and background

适用范围：本指南旨在提供生物制药行业中一次性使用生物工艺系统使用伽马射线进行微生物控制和灭菌的基本信息和建议。

Scope of application: The purpose of this guide is to provide basic information and recommendations for the use of gamma radiation for microbial control and sterilization in the biopharmaceutical industry.

虽然电子束辐射类似于 γ 射线辐射照并遵循相同的标准，由于其有限的穿透能力它一般不用于一次性使用系统的微生物控制或灭菌由于其有限的穿透能力单次使用系统，因而是不考虑本文件中。

Although electron beam radiation is similar to gamma ray radiation and follows the same criteria, it is generally not used for the microbiological control or sterilization of single-use systems due to its limited penetrating power. Because of its limited penetrating ability, single-use systems, therefore It is not considered in this document.

用途：BPSA 辐照灭菌小组委员会意在本指南中提出以下：

Uses: The BPSA Radiation Sterilization Subcommittee proposes the following in this guide:

•教育读者伽马辐射的和减少或消除生物负荷的一次性生物系统的两种方法来：微生物控制和灭菌验证。

• Two ways to educate readers about gamma radiation and disposable biosystems that reduce or eliminate bioburden: Microbiological control and sterilization validation.

•使读者了解微生物控制和验证灭菌之间的差异，区分在哪里适用于一次性使用的生物制药行业，做出相关实验是足够的，或在不同的生物制药生产过程的应用程序所需的教育决策。

• Make readers aware of the differences between microbiological control and validated sterilization, distinguish where applicable to the single-use

biopharmaceutical industry, make relevant experiments that are sufficient or required for applications in different biopharmaceutical production processes Education decision.

•总结的标准方法医疗产品灭菌用γ辐射，这对于生物制药行业公认的适用于单次使用系统的验证。

• Summarize the standard method of sterilization of medical products with gamma radiation, which is recognized by the biopharmaceutical industry for verification of single-use systems.

•提供在验证生物过程组件和系统的辐射灭菌使用的生物负载和无菌试验方法的建议。

• Provides recommendations for bioburden and sterility testing methods used in validation of radiation sterilization of biological process components and systems.

背景：行业标准的医疗灭菌验证

Background: Industry-standard medical sterilization verification

产品辐射已建立组织，如美国国家标准学会（ANSI），该协会推进医疗器械（AAMI），国际组织标准化组织（ISO）和 ASTM 国际组织。在生物制药和生物技术药物工业的进步已导致需要预先灭菌或微生物控制的产品，可以在关键制造工艺被直接引入。最初，这些一次性产品进行了有针对性的小规模应用，例如实验室规模的药物开发和临床前研究。在最近几年中，在临床和过程尺度单次使用的一次性产品线，包括高区滤波器胶囊，膜层析单位，管路，连接器和柔性生物器皿（例如，聚合物膜袋）中以指数增长。对于辐照灭菌验证既定的行业标准医疗产品已成功地应用于此类产品时，无菌验证所需和设备和药品监管机构以对此认可。灭菌验证标准的医疗产品生物工艺系统中的应用，然而，可能相当昂贵和复杂的。由于本指南中进一步讨论，使用模式的主站系统，通过标准的支持，可以减轻这些负担，或无辐射无菌验证可能的情况下被使用，其中一个高却未确定微生物的控制程度是足够。关键定义在“词汇表”中提出。

Product radiation has established organizations such as the American National Standards Institute (ANSI), which promotes medical devices (AAMI), the International Organization for Standardization (ISO) and ASTM International. Advances in the biopharmaceutical and biotech drug industries have led to the need for pre-sterilized or microbially controlled products that can be directly introduced in key manufacturing processes. Initially, these disposable products were targeted for small-scale applications such as laboratory-scale drug development and preclinical studies. In the last few years, single-use disposable product lines at the clinical and process scales, including high zone filter capsules, membrane chromatography units, tubing, connectors, and flexible biological vessels (eg, polymer membrane bags) With an exponential increase. For radiation sterilization, verifying that established industry-standard medical products have been successfully applied to such products, sterility verification needs and equipment and drug regulatory agencies recognize it. The sterilization validation standard for medical product biotechnology applications, however, can be quite expensive and complicated. Because of the further discussion in this guide, the use of the master mode of the system, through the standard support, can reduce these burdens, or no radiation Sterility testing is used where possible, where a high but undefined microbial control is sufficient. Key definitions are presented in the "Glossary".

γ辐射基础知识

Basic knowledge of gamma radiation

γ辐射是电磁辐射的应用（射线）从放射性核素如钴 60（60 Co）的和铯 137（137Cs 的）同位素发射。伽马射线不会被大多数材料阻碍，并且可以穿透大多数一次性生物过程系统组件。电离辐射是通过破坏核酸导致微生物核酸失活。γ射线也不会被物质保留，没有留下任何残留的放射性。 γ辐射剂量的单位是千戈瑞（kGy 的），是其量化的辐射所吸收的能量。一灰度是辐射能量的 1 焦耳由 1 千兖物质（一个千戈瑞= 1 焦耳/兖）的吸收量。剂量≥8 千戈瑞，通常足以消除低生物负荷水平（表 9 中的参考 2）。在生物负荷级别升高中（> 1000 菌落形成单位或 cfu 的，每单位），可能需要更高的剂量达到无菌。通常，25kGy 的可实现无菌 10-6 无菌保证水平（SAL）。即使有较高的生物负载水平，可以减少

生物负荷以较低的概率来实现无菌（例如，SAL 10-5 或 10-4）。照射到这种 SAL 水平的产品仍是无菌的，但是非无菌的概率仍然较高，可能不符合在行业标准的规定确认要求无菌标准灭菌医疗产品的伽马辐照过程使用明确定义的操作参数来确保准确的剂量。在设计良好的辐照设施，用于材料的任何给定密度的唯一变量确定辐射的产品和微生物接受的量时的辐射场中的材料花费。产品不暴露于热，湿度，压力或真空。 γ 射线照射产生的废物最小副产物和不需要隔离除气（如用环氧乙烷气体灭菌）或例行生物反应测试。作为一个恒定和可预测的灭菌方法，伽马辐照安全，省时和降低成本效益。除了微生物失活，γ辐射也引起电离聚合物分子和激发（7）. 随着时间的推移和依赖于剂量，被吸附的剂量可导致改变聚合物的物理或化学性质。有些聚合物表现出较高的电阻比其他辐照诱发变化，但是所有的聚合物都受到一定的影响。而 25 千戈瑞的最小剂量所需的微生物控制和灭菌，实际应用的剂量通常是在 25-50 千戈瑞范围。这是是要注意的，辐射的吸附是累积的，并且一些聚合物可适合在伽马辐照一次性生物过程系统的使用可能不能够承受超过 50 千戈瑞，并且随时间仍然保持它们的完整性。因此，应避克反复照射(8).

Gamma radiation is the application of electromagnetic radiation (rays) emitted from radioisotopes such as cobalt 60 (60 Co) and cesium 137 (137Cs) isotopes. Gamma rays are not obstructed by most materials and can penetrate most disposable bioprocess system components. Ionizing radiation causes the inactivation of microbial nucleic acids by destroying nucleic acids. Gamma rays are also not retained by matter, leaving no residual radioactivity. The unit of gamma radiation dose is kGy, which is the energy absorbed by its quantified radiation. A gray scale is the amount of 1 Joules of radiation energy absorbed by one thousand gallons of material (one thousand Gore = 1 Joule/Kelvin). A dose of ≥8 kGy is usually sufficient to eliminate low bioburden levels (Reference 2 in Table 9). In an elevated bioburden level (>1000 colony forming units or cfu per unit) higher doses may be required to achieve sterility. Typically, a sterile 10-6 Aseptic Assurance Level (SAL) is achievable at 25 kGy. Even with higher bioburden levels, bioburden can be reduced with a lower probability of achieving sterility (for example, SAL 10-5 or 10-4). Irradiate this SAL

The level of product is still sterile, but the probability of non-sterility is still high, may not meet the requirements of the industry standard to confirm the requirements of the sterilized standard sterilized medical products gamma irradiation process using well-defined operating parameters to ensure accurate dose. In a well-designed irradiation facility, the only variable for any given density of material determines the material cost in the radiation field when the irradiated product and the amount accepted by the microorganism are determined. The product is not exposed to heat, humidity, pressure or vacuum. The minimal byproducts of waste generated by gamma irradiation and the need for isolated degassing (such as sterilization with ethylene oxide gas) or routine biological reaction tests. As a constant and predictable sterilization method, gamma irradiation is safe, time-saving and cost-effective. In addition to microbial inactivation, gamma radiation also causes ionizing polymer molecules and excitation (7). Over time and depending on the dose, the absorbed dose can result in changing the physical or chemical properties of the polymer. Some polymers exhibit higher resistance than other radiation-induced changes, but all polymers are affected. While the minimum dose of 25 kGy required for microbial control and sterilization, the actual dose applied is usually in the 25-50 kG range. It is to be noted that the adsorption of radiation is cumulative and that some polymers may be suitable for use in gamma irradiation. The use of one-off biological process systems may not be able to withstand more than 50 kGy and still maintain their integrity over time. Therefore, we should avoid repeated irradiation (8).

微生物控制和灭菌

Microbial control and sterilization

一般概念的由 γ 照射在当前的工业标准中所述的医疗产品灭菌协议可以直接应用到一次

性生物过程系统。这些行业标准要求的效果和灭菌过程的重复性的确认，根据该判定平均生物负载和系统最小的辐射剂量照射后，随后的无菌试验。经过验证的无菌系统也受到例行审计，涉及到生物负荷和无菌试验。标准程序进行伽马灭菌验证和分别应用到在第 6 和 7 一次性生物过程系统中概括。这些标准对在小型定制批量制造，特别是对于在使用样品系统生物处理系统中的应用临床前或临床药物开发过程中，可能是昂贵和繁琐，可能需要的最终产品设计灭菌重新验证。作为替代的无菌标签认证要求，许多生物过程的系统可以被适当微生物简单地通过照射控制典型地在 25 千戈瑞根据范围剂量，且标准方法进行灭菌验证可能并不必需的。最低 25 千戈瑞剂量灭菌索赔源于查尔斯 Artandi 和沃尔顿凡温兖尔在 1959 年进行的一项研究的作者确定的“最低剂量杀死”超过 150 种不同的微生物。由于他们的研究结论，他们选择了 25 千戈瑞作为灭菌剂量，指出“[25 千戈瑞]是最小杀死最顽固的 40％以上，微生物“(9)。因此，25 千戈瑞成为确立为适合的最小照射量进行灭菌。25 千戈瑞这一历史灭菌剂量也可足以消除存活的生物负载和提供微生物控制高水平时，不需要经过验证的无菌要求。部件或要求零或低生物负荷时在非无菌过程施加不需要验证无菌要求和作为微生物控制可能是合格的系统。该以下部分旨在帮劣读者判断是否验证杀菌，或者更简单地说，微生物控制，是合适的。

The general concept of medical product sterilization protocols described by current gamma irradiation in current industry standards can be directly applied to disposable biological process systems. These industry standards require the validation of the effects and reproducibility of the sterilization process, based on which the average bioburden and the system's minimum radiation dose are irradiated after the subsequent sterility test. The validated sterile system is also subject to routine audits involving bioburden and sterility tests. Standard procedures were performed for gamma sterilization validation and applied separately to the 6th and 7th disposable biological process systems. These standards for pre-clinical or clinical drug development applications in small-scale custom batch manufacturing, particularly for use in a sample system biological treatment system, it can be expensive and cumbersome, and final product design sterilization re-verification may be required. As an alternative to aseptic labeling requirements, many biological process systems can be controlled by appropriate microorganisms, typically at 25 KGy doses under irradiation, and sterilization verification by standard methods may not be necessary. The minimum 25-kilo-Greie dose sterilization claim originated from Charles Artandi and Wall. The authors of a study conducted by Dun Van Winger in 1959 identified "lowest dose killing" of over 150 different microorganisms. As a result of their research, they chose 25 kGy for the sterilization dose, stating that "[25 kGy] is the least resistant to killing more than 40% of the most intractable microorganisms" (9). As a result, 25 kGy was established as a suitable minimum exposure for sterilization. The historical sterilant dose of 25 k Gei can also be sufficient to eliminate surviving bioburden and provide high levels of microbial control without the need for validated sterility requirements. Components that require zero or low bioburden when applied in a non-sterile process do not require verification of sterility requirements and may be a qualified system as a microbial control. The following sections are intended to help readers determine whether to verify sterilization, or more simply, microbial control, is appropriate

生物负荷控制在一次性使用的系统生物负荷控制单机的使用

Bio-load control in the use of single-use system bio-load control stand-alone

在生物制药生产，其中药物产品是由细胞培养物产生的，可以分为四个处理的阶段（图 1）。在上游阶段，营养物质和其它流体，随着生产细胞，被引入一个发酵罐或生物反应器中，并将细胞产生目标分子。在收获阶段，将细胞使用离心分离靶分子，深层过滤或膜过滤分离。在下游级中，目标分子进行一系列的分离，纯化，并应用色谱法和膜过滤，以最终产生的纯化的原料到达药产品浓度级。在最终制剂和填充阶段中，纯化的整体（活性药物成分（API）或生物）中的最

终液体制剂的制备，过滤灭菌，或在无菌条件下填充到最终无菌容器中。后者阶段是类似于如何合成医药用无菌工艺制造。在这些阶段的过程中，持续需要微生物控制，以防止不良的污染。国际上规定指出，无菌工艺必须进行验证，以支持灭菌要求。这并不适用，要处理为微生物控制，也可以具有零或低生物负荷，但尚未得到证实具有限定 SAL。虽然无菌来保证通过验证以提供所需的原料作为最终灭菌制剂和灌装注射药品和生物制品，生物过程中的许多制造阶段的制备和消毒（图 1）难以消毒和可能不需要实际验证无菌。相反，它们是根据微生物控制的操作时，如可通过γ照射未经灭菌的验证来提供。考虑是否一个处理步骤，必须验证为无菌的，在维持控制的微生物（零或低生物负荷）状态下，对优化的时间和成本的要求进行工艺开发的关键对比。同样，当验证无菌性是必需的，考虑是否需要一个完整的一次性的系统或只流体路径被确认为无菌也可以影响时间和成本的要求。如前所述，建立和维持无菌为单次使用生物过程系统组件或组件的验证要求可以要求将他们的用户进行最终承担显著成本。特别是在随后的生产过程中的工艺开发和，微生物控制的基础上照射要求可足以防止显著微生物污染，同时节省了时间保持一个有效的无菌要求的成本。一个经审定的无菌要求和实质增加的成本来实现这一保证提供的补充保障之间的平衡是一个必须由生物制药生产商进行。在必须作出选择时最有可能被各单元操作的风险评估驱动以及制造过程作为一个整体。在上游加工，细菌（例如，大肠杆菌）细胞培养物倾向于在很短的时间操作，并是对过度生长相当耐受污染物的细菌的低水平。在这种情况下，一个用户可能认为一次性的在单次使用系统制备一次性生物反应器和培养基或其它营养添加剂可根据未经灭菌验证所提供的照射微生物控制可以安全地操作。哺乳动物细胞培养物，相比之下，通常延长的时间周期（例如，两个运行周）一般被细菌污染更敏感。在这样的情况下，通过灭菌验证来提供额外的保证有效验证，虽然无菌控制经γ-辐射得到提高，但不确定的概率可以是发展，甚至在生产过程中加强的。尤其是在发展的过程中细胞收获和下游加工步骤（离心，深度或膜过滤，并层析，用中间控股）很少。相反，工艺设备化学消毒或消毒，并保持为微生物控制了零或低生物负荷。中间搁置可以保持在低的温度，以防止微生物生长又一个非无菌处理步骤。在未要求保护的这些工艺步骤是无菌的情况下，没有必要验证无菌一次性系统的制备方法缓冲供料溶液或中间含有。缓冲溶液或中间体通过照射生物负荷减少过滤系统过滤为微生物控制生长通常适用于不验证为无菌的工艺步骤。 为制定和填充还提供了选项，以辐射无菌的验证和控制微生物之间进行选择。当无菌成品散装的活性药物成分或生物存储降低的温度下随后的处理，包括制剂，灭菌过滤，并最终无菌灌装，预过滤存储之前在微生物控制的容器可能是足够的。明确规定一次性使用系统的唯一关键步骤被确认为无菌是在准备无菌的 API 和无菌灌装无菌容器；也就是说，如果该流体是被要求作为无菌的，则一次性系统它填充到必须具有验证要求。

In biopharmaceutical production, where the drug product is produced by cell culture, it can be divided into four stages of treatment (Figure 1). In the upstream phase, nutrients and other fluids, with the production of cells, are introduced into a fermenter or bioreactor and the cells produce the target molecule. During the harvest phase, the cells are separated by centrifugation of target molecules, deep filtration or membrane filtration. In the downstream stage, the target molecule undergoes a series of separations, purifications, and chromatography and membrane filtration to produce the final, purified raw material that reaches the drug product concentration level. In the final formulation and filling phase, the final liquid formulation in the purified whole (active pharmaceutical ingredient (API) or biological) is prepared, filter sterilized, or filled into a sterile final container under aseptic conditions. The latter stage is similar to how synthetic medicines are manufactured using a sterile process. In the course of these phases, there is a continuous need for microbial control to prevent undesirable pollution. International regulations state that aseptic processing must be validated to support sterilization requirements. This does not apply. To be treated as microbiological control, it is also possible to have a zero or low bioburden, but it has not yet been

demonstrated that there is a defined SAL. Although sterility is guaranteed to pass the verification to provide the required raw materials as final sterilized preparations and to inject injected medicines and biological products, the preparation and disinfection of many manufacturing stages in biological processes (Fig. 1) is difficult to sterilize and may not require actual verification Sterile. Instead, they are provided according to microbiologically controlled operations, such as verification by gamma irradiation without sterilization. Consider whether a process step must be validated as sterile, with a key contrast in process development between the controlled microbiological (zero or low bioburden) states and the time and cost requirements for optimization. Similarly, when verification of sterility is required, consideration of whether a complete disposable system is required or only the fluid path is confirmed as sterile can also affect the time and cost requirements. As mentioned earlier, establishing and maintaining sterility as a single use of the validation requirements for components or components of a biological process system can require that their users ultimately bear significant costs. Especially in the subsequent process of process development and microbiological control, the irradiation requirements can be sufficient to prevent significant microbial contamination, while saving the cost of maintaining an effective sterile requirement. The balance between increased costs to achieve this assurance provides a balance between supplemental protection is a must for biopharmaceutical manufacturers. When the choice must be made, it is most likely to be driven by the risk assessment of each unit operation and the manufacturing process as a whole. In the upstream processing, bacterial (e.g., E. coli) cell cultures tend to operate in a short period of time, and are low levels of bacteria that over-grow well tolerant contaminants. In this case, a user may think that a one-time use of a single use system to prepare disposable bioreactors and culture media or other nutritive additives can be safely handled according to the irradiation microbe control provided without sterilization verification. Mammalian cell cultures, by contrast, are generally more susceptible to bacterial contamination than extended periods of time (eg, two run weeks). In such cases, verification is provided by sterilization to provide additional assurance that effective testing, although aseptic control is enhanced by γ-irradiation, the uncertain probability can be developed and even enhanced during the production process. Especially in the course of development cell harvesting and downstream processing steps (centrifugation, depth or membrane filtration, and chromatography, with intermediate holdings) are rare. Instead, the process equipment is chemically disinfected or sterilized and maintained as a microorganism controls zero or low bioburden. The middle shelf can be kept at a low temperature to prevent microbial growth and a non-sterile treatment step. In the event that these unprotected process steps are sterile, it is not necessary to verify the preparation of the sterile disposable system buffered feed solution or intermediate containment. Buffered solutions or intermediates are filtered through an irradiating bio-load reduction filter system. Microbial growth control is generally applied to process steps that are not validated as sterile. For the formulation and filling also offers the option to choose between radiation-sterile validation and control of microorganisms. Subsequent processing, including formulation, sterilization filtration, and ultimately aseptic filling of the aseptically finished active pharmaceutical ingredient in bulk or at a reduced temperature of biological storage, may be sufficient in a microbially controlled container prior to pre-filter storage. The only key step that clearly stipulates a single-use system is identified as sterility in preparation of sterile API and aseptically filled sterile containers; that is, if the fluid is required to be sterile, a disposable system It is populated to have verification requirements.

当前对于灭菌验证的标准

Current standards for sterilization verification

一些行业标准，可用于伽玛辐照保健产品灭

菌验证。在 ANSI / AAMI / ISO 11137：2006 标准（灭菌的保健品 - 辐射）最初发表于 1994 年，随后由 ISO 和 AAMI 开发了多种配套技术报告。关键在这些是 AAMI 技术信息报告（TIR）33：2005 年在选定的灭菌剂量的实体化 - 法 VD 最大（10）在 ISO 的系统回顾 11137：1994（在美国通过了 ANSI / AAMI / ISO 11137：1994），该文件被修改，并在总标题分为三个部分，保健产品的灭菌 - 辐射的 ANSI / AAMI / ISO 11137 的三个部分：比 2006 年的描述。第 1 部分：开发，验证和灭菌过程的医疗器械常规控制的要求规定了开发，验证，流程控制和常规监测的辐射灭菌的保健产品的需求。第 1 部分适用于使用放射性核苷酸 60 Co 或 137 Cs 的连续和间歇式的γ辐照器，并且使用一个光束辐照从电子或 X 射线发生器。第 2 部分：灭菌剂量的确定描述的方法可以用于确定所需的最小剂量以达到无菌性的规定的要求，包括方法，以证实 15 或 25 千戈瑞作为灭菌剂量。第 3 部分：指导剂量学方面提供了指导剂量为保健产品，并建立了最大剂量（产品认证）的剂量学方面的辐射灭菌;建立灭菌剂量;安装资格;经营资格;和性能鉴定。ANSI/ AAMI / ISO 标准描述了两种方法进行灭菌验证：

Some industry standards can be used for sterilization verification of gamma radiation health products. The ANSI / AAMI / ISO 11137:2006 standard (sterilized health supplements - radiation) was originally published in 1994, followed by a variety of supporting technical reports developed by ISO and AAMI. The key in these are the AAMI Technical Information Report (TIR) 33: Substantialization of selected sterilization doses in 2005 - Method VD Max (10) In ISO System Review 11137:1994 (US/ANSI/AAMI/ISO passed in the United States 11137:1994), the file was modified and the overall heading is divided into three sections, Sterilization of Health Products - Radiation's Three Parts of ANSI/AAMI/ISO 11137: Descriptive Than 2006. Part 1: Requirements for routine control of medical devices during development, validation, and sterilization processes dictate the need for radiation-sterilized healthcare products for development, verification, process control, and routine monitoring. Part 1 applies to continuous and batch gamma irradiators using radioisotope 60 Co or 137 Cs, and uses a beam to irradiate electrons or X-ray generators. Part 2: Determination of Sterilization Dose The described method can be used to determine the minimum dose required to achieve the specified requirements for sterility, including methods to confirm 15 or 25 kGy as the sterilization dose. Part 3: Guided dosimetry aspects provide guidance doses for health care products, and establish maximum dose (product certification) of dosimetric aspects of radiation sterilization; establishment of sterilization doses; installation qualifications; business qualifications; The ANSI/AAMI/ISO standard describes two methods for sterilization validation:

•剂量设定的方法（方法 1 或方法 2，ANSI / AAMI / ISO 11137），它考虑到分布和产品生物负载的抗辐射性，并且在有限的程度，最终使用的产品，以及

• The dose setting method (Method 1 or Method 2, ANSI/AAMI/ISO 11137), which takes into account the radiation resistance of the distribution and product bioburden, and to a limited extent, the final use of the product, and

•剂量属实方法，（VD 最大值的方法），这意味着实验设计来限定预定的伽马剂量作为灭菌剂量（1-3）。

• Dosage is a faithful method, (method of maximum VD), which means that the experiment is designed to define a predetermined gamma dose as the sterilization dose (1-3).

其中一些方法' 相似之处包括：

Some of these methods' similarities include:

•只有结合适当的质量管理体系的应用

• Only apply the application of an appropriate quality management system

•承认的剂量控制和生物负荷控制是两个同等重要的方面保证无菌

• Admitted dose control and bioburden control are two equally important aspects of aseptic assurance

•要求通过定期测试论证持续有效性以验证建立辐照灭菌剂量保持适宜产品灭菌。

• It is required to demonstrate continuous

effectiveness through regular tests to verify the establishment of irradiation doses to maintain proper product sterilization.

表 1 总结了额外的相似性和的各种方法的差异。虽然这说明了不同的主要属性方法，请参考实际 ANSI / AAMI / ISO 标准或 AAMI TIR 为综合信息。总的来说，这些方法为用户提供了一定程度的应用来限定照射工艺标准的灵活性，以表示该产品是不是所有的制造和在统一的情况下商业化。用户被赋予范围做出决
定务实，只要他们遵守技术的正确性在几个关键领域：

Table 1 summarizes the additional similarities and differences in the various methods. Although this illustrates different main attribute methods, please refer to the actual ANSI/AAMI/ISO standards or AAMI TIR for comprehensive information. In general, these methods provide the user with a degree of application to define the flexibility of the irradiation process standard to indicate whether the product is manufactured in all cases and commercialized under uniform conditions. Users are given scope to make decisions
Be realistic, as long as they adhere to the correctness of the technology in several key areas:

•灵活性组件，如独立包装的消毒单元，试剂盒和组件

• Flexible components, such as individually packaged disinfection units, kits and components

•灵活性来限定一个单元的一部分的整个装置或灭菌（例如，只有流体通道）

• Flexibility to define the entire device or sterilization of a part of a unit (for example, only fluid channels)

•使用所需要的照射周期资格的产品样本大小。

• Use the required sample size of the product for the required exposure period.

•可接受的生物负荷水平灭菌

• Acceptable bioburden level sterilization

•审计抽查的频率（定期进行，以支持继续使用已建立的灭菌剂量）。虽然 AAMI TIR33：2005 和 ANSI / AAMI / ISO 11137 标准的最初开发重点放在医疗器械行业，他们也适用于生物过程的系统和组件。本指南的其余部分，因此建立在这些行业标准。

• Frequency of audit sampling (periodically to support the continued use of established sterilization doses). Although the initial development of the AAMI TIR33:2005 and ANSI/AAMI/ISO 11137 standards focused on the medical device industry, they also apply to systems and components of biological processes. The rest of this guide is therefore based on these industry standards.

剂量设定方法

Dose setting method

剂量设定方法需要实验，导致无菌产品的生产有资质最小辐射剂量。 2006 和包括：当使用这种类型的方法的常规方法在 ANSI / AAMI/ ISO11137 中描述以下步骤：

The dose setting method requires experimentation that results in the production of a sterile product with a qualified minimum radiation dose. 2006 and include: The following steps are described in ANSI/AAMI/ISO11137 when using the general method of this type of method:

1. 确定目标 SAL。

Determine the target SAL.

2. 获取产品指定数量从三个生产批次的（表 1）的检测。

Get the product specified number of tests from the three production batches (Table 1).

3. 实验确定平均生物负载下 ANSI/ AAMI/ ISO11737-1（11-12）。

Experiment to determine the average bioburden under ANSI/AAMI/ISO11737-1 (11-12).

4. 确定适合生物负载验证剂量。

Determine the appropriate bioburden verification dose.

5. 执行剂量验证研究（照射和无菌试验）.

Perform dose verification studies (irradiation and sterility tests).

词汇：

vocabulary:

无菌操作：从技术上讲，无疾病的微生物。在生物加工应用中，它指的是在一个执行的操作受控环境或具有与门设计的连接器，以防止污染通过引入微生物（可以是无菌的或微生物控制）。

septic processing: Technically, disease-free microorganisms. In bioprocessing applications, it refers to a controlled environment in which an operation is performed or a connector designed with an AND gate to prevent contamination by introduction of microorganisms (which can be sterilized or microbiologically controlled).

生物负荷：在一个产品的活性微生物种群。在杀菌的情况下，它应当立即确定前消毒。生物负载可以在一个项目来描述其全部内容，包括外表面，或只流体接触表面。

Bioburden: Active microbial population in a product. In the case of sterilization, it should be immediately determined before disinfection. Bioburden can describe its entire content in a project, including the outer surface, or only the fluid contact surface.

生物加工组件：一次性使用的部件，模块，或一个系统，其可以包括但不各款局限于过滤器，膜色谱单元，管道，连接，接头，柔性袋子或刚性容器和探针。

Bioprocessing components: single-use components, modules, or a system that can include, but are not limited to, filters, membrane chromatography units, tubing, connections, connectors, flexible bags, or rigid containers and probes.

生物加工系统：一个组合或者生物过程的组合组件旨在促进药物的处理或生物溶液中的单次使用的一次性的格式。系统一个生物负荷减少/微生物之前可以预先装配控制步骤或装配由用户通过连接预灭菌通过使用无菌连接组件。

Bioprocessing system: A combinatorial component of a combinatorial or biological process designed to facilitate the handling of drugs or single-use disposable formats in biological solutions. A bioburden reduction/microbiology system can be pre-assembled with control steps or assembled by the user by connecting pre-sterilized by using a sterile connection assembly.

剂量发布：该产品是无菌的测定基于物理照射处理数据，而不是无菌性测试。

Dose Release: This product is a sterile assay based on physical irradiation processing data, not sterility testing.

假阳性无菌测试结果：测试结果是不正确解释为指示该测试物品有可行生物和该制品是不是无菌的。通常，这样的结果来源于故障处理样品或测试执行 或从一个样品和微生物的生长之间的相互作用介质导致的介质变得浑浊。

False Positive Aseptic Test Results: Test results are incorrectly interpreted as indicating that the test article has a viable organism and the article is not sterile. Typically, such results result from the failure of the treated sample or from the interaction of the medium with the test or from the interaction between a sample and the growth of microorganisms.

照射：应用电离辐射能够摧毁细菌含量。

Irradiation: The application of ionizing radiation can destroy the bacteria content.

微生物控制：产品处于受控干净大会环境随后暴露于伽马辐射。此工艺减少生物负荷负载，但不支持“无菌”标签要求。

Microbial control: The product is exposed to gamma radiation in a controlled clean assembly environment. This process reduces the bioburden load but does not support "sterile" labeling requirements.

例题部分（SIP）：一个产品装配的定义部分或组件。

Sample Part (SIP): A defined part or component of a product assembly.

无菌：不含活微生物。

Sterile: Does not contain live microorganisms.

无菌保证水平（SAL）：无菌保证水平（SAL）：在实践中，无菌状态不能被证明。相反，无菌表示为概率单个活微生物的后发生的一个项目灭菌（1）。通常该术语表示为 10-n, 不作为绝对值。

Sterility Assurance Level (SAL): Aseptic Assurance Level (SAL): In practice, sterility cannot be demonstrated. In contrast, sterility is expressed as a probability that one single item of live microorganisms will sterilize (1). Usually this term is expressed as 10-n, not as an absolute value.

菌测试：测试以确定是否可行微生物存在。通常，该测试涉及浸渍组件或系统或冲洗的流体路径不无菌微生物生长介质，所述介质的下孵育条件

有利于微生物的生长，并观察混浊或微生物生长的后一个合适的其他指示潜伏期。

Bacteria test: Test to determine if viable microorganisms are present. Typically, the test involves impregnating the assembly or system or rinsing the fluid path with a non-sterile microbial growth medium, the lower incubation conditions of said medium facilitating the growth of microorganisms, and observing a suitable other indication latency of turbidity or microbial growth.

杀菌：用于渲染产品中使用经过验证的方法从活微生物。人们普遍认为的末端消毒单位看来是无菌达到无菌保证水平≤的 10-6;即，小于或等于一个机会在概率百万，一个可行的微生物存在于所述灭菌单元（1-6）。较低的 SAL 可以验证在某些情况下无菌（2）。

Sterilization: Used to render products from live microorganisms using proven methods. It is generally believed that the terminal disinfection unit appears to be aseptically achieving a level of aseptic assurance ≤ 10-6; that is, less than or equal to one chance at a probability of one million, and a viable microorganism is present in the sterilization unit (1-6). Lower SALs can verify aseptic (2) in some cases.

验证：建立文件化的证据，可提供高保证程度，一个特定的过程将持续产生产品符合其预定规格和质量属性.

Verification: Establishing documented evidence that provides a high level of assurance that a particular process will continue to produce products that meet their intended specifications and quality attributes.

图 1：使用基本上所有的一次性设备典型的生物过程的示意图（例外包括离心分离机，层析柱，以及用于切向不锈钢持有者流过滤盒或深度过滤器）;在上游和配方，并填写步骤中使用的设备可能需要无菌的验证（由虚线指示），但设备有更大致的收获和下游阶段可能需要照射只在≥25 千戈瑞剂量要求的微生物控制，和灭菌验证（由实心或虚线所示）.

Figure 1: Schematic representation of a typical biological process using virtually all disposable equipment (exceptions include centrifuges, columns, and flow filters or depth filters for tangential stainless steel holders); upstream and formulation , and fill in the equipment used in the step may require sterility verification (indicated by dashed lines), but the equipment has a more general harvest and the downstream stage may need to be irradiated only at the ≥25 kGy dose required for microbial control, and sterilization verification (Shown in solid or dashed lines).

6. 解释结果 – 接受或拒绝研究。

Interpret results - Accept or reject the study.

7. 建立最小剂量消毒，基于所述生物负载和 SAL 要求。

Establish minimum dose disinfection based on the bioburden and SAL requirements.

8. 定期研究所审计剂量测试持续有效性。剂量设定方法涉及剂量基于所述资格微生物的实际辐射抗性分离出产物。其结果是，这些方法提供了可能的最低剂量，但需要更多的产品样本比的剂量属实方法。

Regularly study the effectiveness of the audit dose test. The dose setting method involves the dose separating the product based on the actual radiation resistance of the qualifying microorganism. As a result, these methods provide the lowest possible dose, but require more product samples than the dose-based method.

剂量正确方法

Dosage correct method

在 ANSI / AAMI / ISO 11137-2：2006 VD 最大方法论允许两个预先制定的辐照灭菌剂量消毒：15 千戈瑞和 25 千戈瑞。 AAMI TIR33：2005 年提供了使用七个额外灭菌剂量的灵活性：17.5，20，22.5，27.5，30，32.5，35 千戈瑞。灭菌剂量的范围从 15 千戈瑞的生物负荷高达 1.5 菌落，25 千戈瑞的生物负荷高达 1,000 CFU 和 35 千戈瑞的生物负载高达 440000 cfu。制造商应在其生产过程中的每个阶段都保持严格的生物负荷控制。除了追加剂量设定点，ANSI / AAMI / ISO 11137-2：2006 和 AAMITIR33：2005 年，基于相同的原理，并提供基本相同的指导。使用 VD 最大方法时的一般方法包括以下步骤：

The ANSI/AAMI/ISO 11137-2:2006 VD

Maximum Methodology allows for the sterilization of two pre-established irradiation sterilization doses: 15 kGy and 25 kGy. AAMI TIR33: 2005 provided the flexibility to use seven additional sterilization doses: 17.5, 20, 22.5, 27.5, 30, 32.5, 35 kGy. Sterilization doses range from 15 kGy bioburden up to 1.5 colonies, 25 kGy bioburden up to 1,000 CFU, and 35 kGy bioburden up to 440,000 cfu. Manufacturers should maintain strict bioburden control at each stage of their production process. In addition to the supplemental dose setpoints, ANSI/AAMI/ISO 11137-2:2006 and AAMITIR33:2005 are based on the same principles and provide basically the same guidance. The general method when using the VD max method includes the following steps:

1. 从产品获取三个生产批次检验。

Obtain three production lot inspections from the product.

2. 实验确定平均生物负载。生物负载估计必须满足的标准所选择的 VD 最大剂量。

Experiment to determine the average bioburden. The maximum dose of VD selected by the criteria that the bioburden estimate must satisfy.

3. 确定适当的验证照射剂量平均生物负载。

Determine the appropriate bioburden to verify the irradiation dose.

4. 执行剂量验证研究（辐照和无菌试验）

Perform dose verification studies (irradiation and sterility tests)

5. 解释结果 - 接受或拒绝研究结果。

Interpret Results - Accept or reject the results of the study.

6. 接受或拒绝所述预定辐射剂量的最低剂量的灭菌。

Accept or reject the lowest dose of sterilization of the predetermined radiation dose.

7. 定期研究所审计剂量测试持续有效性。在 VD 方法最大的佐证辐照灭菌剂量达到 10-6 的 SAL;不受该方法支持目前更高的 SAL（更低保证无菌的）。固定剂量键控关闭的两个输入：生物负载数（实验确定的）和最坏情况下的生物负载电阻数据驱动假设（2）。虽然在 AAMI TIR33 灭菌剂量的选择：2005 是固定的，采样要求比方法 1 和 2 的 ANSI / AAMI / ISO 11137 以下。

Regularly study the effectiveness of audit dose tests. In the VD method, the largest demonstration of irradiation sterilization dose is 10-6 SAL; this method is not supported by the current higher SAL (lower guaranteed sterility). Two inputs for fixed-dose keying off: bioburden (experimentally determined) and worst case bioload resistance data driving assumptions (2). Although the choice of AAMI TIR33 Sterilization Dose: 2005 is fixed, sampling requirements are less than methods 1 and 2 of ANSI/AAMI/ISO 11137.

实施途径验证

Implementation method verification

鉴于它们的尺寸和复杂性，一次性生物过程系统和部件构成过程中的验证测试比较困难。大规模系统可以是，例如，连接到数米的管道，高区域过滤胶囊（s）表示，可以是 254 毫米（10 英寸）或更大的 10,000- L 袋的组件，并不连接器一个复杂的设计 - 或者连接器的复杂歧管。因此，你应该仔细计划一个简单而科学有效的方法，生物负荷和无菌测试。样品项部（SIP）产品分组，和普通方法在 ANSI/ AAMI/ ISO11137 测试说明：2006 准则提供的策略解决的医疗装置的设计和医疗产品的复杂性，并且也适用于大规模生物过程组件和如以下所描述的几节所述的系统。

Given their size and complexity, verification tests in the process of one-off biological process system and component construction are difficult. A large-scale system can be, for example, a pipe connected to several meters, represented by a high zone filter capsule (s), which can be a 10,000-liter bag assembly of 254 mm (10 inches) or more, not a complicated connector. Design - or the complex manifold of the connector. Therefore, you should carefully plan a simple and scientifically effective method for bioburden and sterility testing. Sample Item Division (SIP) product groupings, and general methods in the ANSI/AAMI/ISO11137 test description: The 2006 guidelines provide strategies to address the design of medical devices and the complexity of medical products, and also apply to large-scale biological process components and such

as The system described in the sections described below.

产品分组/系列:

Product grouping/series:

最简单的策略是对三个标准的生产批次采样。通常，多个产品制造商开发的一个或多个产品族不单个产品可以代表其系统（10）的其余成员的状况。用来表示一个产品系统此单品可能被指定“主产品”，一个“同等产品”或“模拟产品。”主产品：主产品不一定是最大的一个系统。在所有的材料和部件相同，并且产品变化仅在材料的大小或量的情况下，主产物通常是最多的一个。 根据包含的材料和制造过程中，主产品可以是一种具有制造和组装，或这些因素的组合中最组件典型操作，材料的最大组合，最高过滤面积。最终，主产物是一个认为最有挑战性的灭菌过程。

The simplest strategy is to sample three standard production lots. Typically, one or more product families developed by multiple product manufacturers not a single product may represent the status of the rest of their system (10). Used to indicate a product system. This item may be designated as the "main product," an "equivalent product," or "simulation product."

Main product: The main product is not necessarily the largest one. Where all materials and components are the same, and the product changes only in the size or quantity of the material, the main product is usually the largest one. Depending on the materials contained and the manufacturing process, the main product can be a combination of manufacturing and assembly, or a combination of these factors, the most typical operation of the assembly, the largest combination of materials, and the highest filtration area. In the end, the main product is a sterilization process that is considered the most challenging.

同等产品： 同等产品不一定是那些拥有相同的生物负荷水平，因为生物负荷水平自然样品和套接管时间样本之间是变化的。产品是否可以视为等同;

The equivalent product: The equivalent products are not necessarily those who have the same bioburden level because the bioburden level varies between the natural sample and the splice tube time sample. Whether the product can be considered equivalent;

•生物负载估计是差不多的;

• The bioburden estimate is similar;

•生物负载特性是相似的;

• Bioburden characteristics are similar;

•生物负载估计结果在灭菌剂量是大约相同的使用方法 1 和方法 2，或验证剂量是大约相同的使用 VDmax 时。

• The bioburden estimate results at approximately the same sterilization dose as Method 1 and Method 2, or verify that the dose is approximately the same when using VDmax.

模拟产品： 一个模拟的产品是一个包含相同的材料和实际产品的组成部分，但已经制造仅用于测试目的，因此不是一个实际的产品。这通常是制成包括或组合产品系列的代表最坏情况下的属性。与模拟产品的组合物或结构不影响剂量判定的正确性。在设计一个模拟的产品，应注意创造一个不产生不适当的挑战，谁执行生物负荷和无菌试验的实验室工作人员。

Analog Products: A simulated product is a component that contains the same material and actual product but has been manufactured for testing purposes only and is therefore not an actual product. This is usually the worst-case property that is made to include or combine product lines. The composition or structure with the simulated product does not affect the correctness of the dose determination. In designing a simulated product, care should be taken to create a laboratory worker who does not produce undue challenges and who performs bioburden and sterility tests.

实施途径测试的大型系统

Large-scale systems for implementing pathway testing

生物负荷和生物工艺系统或存在两个具体的挑战组件的无菌试验。第一，大制品是特别难于操作无菌。具体问题包括引入这种大的物品到生物安全柜，在无菌条件下添加和除去流体至测试物件，在无菌条件下操作所需的测试大流体体积，而对于大的系统提供孵化空间， 用于测试整个产品（而不是单独的流体路径），处理其外

部表面，而不会污染他们的额外的问题，必须加以克服。第二个问题是，生物过程系统或组件往往是相当昂贵的。采取这样的产品在其生命周期的开始以非常低的量出售，测试相对大量实际物品可以是令人望而却步到其商业化的可能性。

Bioburden and bioprocess systems or there are two specific challenge components for sterility testing. First, large products are particularly difficult to handle sterile. Specific issues include the introduction of such large items into biosafety cabinets, the addition and removal of fluids to test items under aseptic conditions, the large volume of test fluid required to operate under sterile conditions, and the provision of incubation space for large systems, The additional problems that are used to test the entire product (rather than a separate fluid path) and treat its exterior surfaces without contaminating them must be overcome. The second problem is that biological process systems or components are often quite expensive. Taking such a product is sold at a very low volume at the beginning of its life cycle, and testing a relatively large number of actual items can be prohibitively commercialized.

具体的方法， 制造商采取来解决这些问题，必须开发专用于每一种情况下， 保持它们之间平衡

The specific method that manufacturers take to solve these problems must be developed specifically for each case to maintain a balance between them

•一个愿望，并以确保技术的正确性通过测试实际的文章，

• A desire, and to ensure the correctness of the technology by testing the actual article,

•为了避免错误结果的愿望（虚增生物负载估计或假阳性无菌试验结果）所造成的不实用操作制品。

• Improper handling of products caused by the desire to avoid erroneous results (inflated bioburden estimation or false positive sterility test results).

几种常见的方法可以减轻由这两个问题所带来的困难。以下实施例旨在说明什么做可以克服的问题;它们不打算排除其它科学辩护的方法。

Several common methods can alleviate the difficulties caused by these two problems. The following examples are intended to illustrate what problems can be overcome; they are not intended to exclude other methods of scientific defense.

样品项目部分（SIP）： 该 SIP 方法允许制造和测试一种缩尺产物。这减少了测试品的成本和在实验室操纵产品的困难。这种方法增加实验通过基于 SIP 的文章和所代表的实际产品之间不同规模倍增确定生物负载估算。SIP 乘法器可通过实验或简单地通过取模型的比率来确定制造的最大系统。

Sample Project Section (SIP): This SIP method allows the manufacture and testing of a scaled product. This reduces the cost of test articles and the difficulty of manipulating products in the lab. This method adds experiments to determine bioburden estimates by multiplying the size between SIP-based articles and the actual product represented. The SIP multiplier can determine the largest system manufactured by experiment or simply by taking the ratio of the model.

流体路径： 在某些情况下，它是适当的，以验证产品的流体路径的无菌。测试流体路径可以比测试整个产品因为一个产品作为更简单

Fluid Path: In some cases, it is appropriate to verify the sterility of the product's fluid path. Testing the fluid path can be better than testing the entire product because one product is easier

一个流体路径通常需要部分地填充所述产品用无菌缓冲的生物负载测试，以确保所有的表面被润湿，然后搅拌该制品通过用手推动悬浮生物体入缓冲区。然后，缓冲器被除去，并测试通过标准的微生物学方法生物负载的负载。为更好地量化生物负荷的手段，开始实际的生物负载研究之前进行生物负载恢复研究。回收研究有两个目的：量化与生物负载从测试条中回收的效率，并帮助确定的具体方法，将在实际中使用生物负载研究。

A fluid path generally requires partial filling of the product with a sterile buffered bioburden test to

ensure that all surfaces are wetted, and then the product is agitated to manually push the suspended organism into the buffer zone. The buffer was then removed and the load of the bioburden by standard microbiological methods tested. To better quantify bioburdens, bioburden recovery studies were conducted before actual bioburden studies were initiated. The recycling study has two purposes: to quantify the efficiency of the bio-load recovery from the test strip, and to help determine the specific method that will be used in the bio-load study.

用于无菌试验，该制品或者部分地填充有微生物生长介质或与提取液。以下的搅拌工序中，生长培养基可以留在内或除去，并测定微生物负载。

For sterility testing, the article is either partially filled with a microbial growth medium or with an extract. In the following stirring process, the growth medium may be left inside or removed, and the microbial load may be measured.

分段大型产品的： 为了有助于操作，大量的产品可以被分成部件更容易操纵在实验室测试或辐照。 如果整个产品，而不是简单地将流体路径是进行测试，这种方法是特别有效的。这种方法的一个例子是切割大型生物容器成 10 个部分，各切割为多个小块并加入片断的容器，很容易在无菌条件下处理的微生物实验室和生物安全柜。在这种情况下，每个容器将被测试，生物负载的总和将代表原始袋的生物负载。同样地，所有 10 个部分需要是无菌的原始生物容器算作无菌的。使用产品包装作为一个容纳器件：一般被两个外包装在生物工艺系统或组件，以确保其清洁和无菌。有些制品，尤其是那些在其整个产品都必须经过测试，非常适合于测试，而他们留在原包装。在这种情况下，内包装作为储存容器。一个小的开口是由在包装进入测试物品和添加或删除缓冲器或生长培养基中。开口比无菌密封以保持一个封闭的系统，并防止微生物污染。该方法是不太有效的试验制品是闭环系统，必须打开以访问内部表面。

Segmented large-scale products: In order to facilitate the operation, a large number of products can be divided into components that are easier to manipulate in laboratory tests or irradiation. This method is particularly effective if the entire product, rather than simply the fluid path is tested. An example of such a method is to cut a large biological container into 10 parts, cut into multiple small pieces each and add a piece of the container, a microbiology laboratory and a biological safety cabinet that can easily be handled under aseptic conditions. In this kind of In case, each container will be tested and the sum of the bioburden will represent the original bag's bioburden. Similarly, all 10 parts need to be sterile as a raw biological container counted as sterile.

The product packaging is used as a containment device: it is generally packaged in two bioprocess systems or components to ensure its cleanliness and sterility. Some products, especially those that have to be tested in their entire product, are very suitable for testing while they remain in the original packaging. In this case, the inner package serves as a storage container. A small opening is included in the package entering the test article and adding or removing a buffer or growth medium. The openings are more sterile than sealed to maintain a closed system and prevent microbial contamination. This method is less effective. The test article is a closed loop system that must be opened to access the interior surface.

剂量释放

Dose release

在排位的伽马辐射微生物控制或灭菌周期，必须有量化的伽玛辐射剂量的手段。这是通过剂量测定完成，场有关吸收的辐射的量化。测量装置被称为剂量计。剂量学有两个方面特别重要：

In the microbiological control or sterilization cycle of the gamma radiation, there must be means of quantifying the dose of gamma radiation. This is done by dosimetry, which quantifies the field's absorption of radiation. The measuring device is called a dosimeter. There are two aspects of dosimetry that are particularly important:

•用于验证特定灭菌剂量的验证剂量必须准确地测量（±10％）

• The verification dose used to verify a specific

sterilization dose must be accurately measured (±10%)

•负载应当剂量映射到保证伽马剂量的均匀性是足够用于进行辐射的配置。

• The load should map the dose to ensure that the uniformity of the gamma dose is sufficient to configure the radiation.

虽然剂量背后科学是超出了本指南的范围，各种剂量的技术存在。 用户应确保剂量计和操作者有资格提供足够的准确度_精确度，尤其是在所考虑的辐射剂量的范围内。这种方法验证的概念应用，因为这将是对哪些产品认证和发布，可以根据任何测量方法屈服的数据。通常情况下，γ 辐照的专业化服务提供商进行资质剂量计。

Although dose behind science is beyond the scope of this guide, various dosage techniques exist. The user should ensure that the dosimeter and the operator are qualified to provide sufficient accuracy and accuracy, especially within the range of radiation dose considered. This method validates the concept of application, as it will be the data on which products are certified and released and can be yielded according to any measurement method. Typically, gamma-irradiated specialized service providers perform qualification dosimeters.

之后的照射周期进行验证，可以在生产中的微生物控制无菌产品的使用。产物被释放剂量测定的基础上，伽马辐照后：一个剂量学验证该循环产生了所需的最小剂量的产品负载。无常规无菌试验需要大量的释放。由于产品发布剂量的，它的制造商必须确保由伽马辐射服务供应商实行的剂量有很好的条件和伽玛辐照操作控制始终如一地提供正确的剂量范围内。

After the irradiation cycle is verified, the microbes in production can control the use of sterile products. The product was released based on dosimetry after gamma irradiation: a dosimetric verification of the cycle produced the required minimum dose of product load. No routine sterility tests require significant release. Due to the product release dose, its manufacturer must ensure that the doses administered by the gamma radiography service providers have good conditions and that the gamma irradiation operation controls consistently provide the correct dose range.

生产决策

Production decision

一次性生物系统代表了显着的益处，以生物制药工艺开发和制造。伴随着好处是在这些系统的采用和整合所有相关者的新的决策。相对于质量属性如微生物控制及灭菌，一些问题可能笼统加以解决，而另一些应在一个特定的生物制药生产过程中加以处理。图 1 提供了决策树杀菌和微生物控制。

Disposable biological systems represent a significant benefit to the biopharmaceutical process development and manufacturing. The benefits are accompanied by the adoption of these systems and the integration of new decisions by all stakeholders. With respect to quality attributes such as microbiological control and sterilization, some problems may be solved in general, while others should be handled in a specific biopharmaceutical production process. Figure 1 provides decision tree sterilization and microbial control.

这个指南提出的有关γ 照射和微生物控制实行一次性生物过程的系统和部件的制造水平的基本问题进行了讨论。它的目的是框架的微生物控制的问题，并作出明智的、合理的决定，以在一次性生物过程系统的制造和使用所需的微生物控制水平提供的结构。

cThis guideline discusses the basic issues related to the level of manufacture of systems and components for the implementation of one-time biological processes for gamma irradiation and microbial control. It is designed to frame the problem of microbial control and make sensible, rational decisions to provide the structure at the level of microbiological control required for the manufacture and use of disposable biological process systems.

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