BEST PRACTICES FOR STERILITY ASSURANCE IN SINGLE-USE PRODUCT MANUFACTURING

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WHAT IS STERILITY?

With the adoption of single use products used in biopharmaceutical production, manufacturers have become increasingly reliant on suppliers for sterile assemblies and components. Sterility can be defined as the absence of microorganisms in or on the various surfaces and within the packaging boundary of the product.

While it is a common belief that merely exposing a single use product to gamma irradiation means the product is sterile, this belief is not factually accurate.

While gamma irradiation is the most used sterilization modality, other modalities include the use of steam, EtO, vaporized hydrogen peroxide (VHP), e-beam and x-ray. Gamma irradiation is the process of using Cobalt 60 rays to penetrate the single use product and kill microorganisms. **While it is a common belief that merely exposing a single use product to gamma irradiation means the product is sterile, this belief is not factually accurate.** Rather, the implementation of sterilized single use product in biopharmaceutical production requires a validated sterility program. This validated sterility program ensures the single use product maintains a sterile packaging envelope and has sterility assurance, a level of confidence that the product is sterile.
A sterility claim for single use product requires a validated sterility assurance level (SAL) of at least 10^{-6} using one of the modalities noted above.

Achievement of SAL 10^{-6} indicates that there is no more than a 1 in 1 million chance of viable organisms being present on the product exposed to the qualified sterilizing modality. In addition to achieving SAL 10^{-6} on the product, a sterility program must ensure that product materials are routinely subjected to the qualified sterilizing modality and that the product packaging envelope is able to maintain a SAL 10^{-6} for the product's life cycle or expiry. Different governing bodies, such as the American National Standards Institute (ANSI), the Association for the Advancement of Medical Instrumentation (AAMI) and the International Organization for Standardization (ISO) provide standards and guidance for sterility program development. Only upon successful program development through qualification testing and routine monitoring, can a single use product be deemed sterile.

PROGRAM DEVELOPMENT

The most common guideline for a validated sterility program is ISO 11137 using the VDmax method. At a minimum gamma irradiation exposure dose of 25 kilograys (kGy), the VDmax method provides a SAL 10^{-6} for a single use product.

> Specifically, CCG's sterility program is based on practices recommended by ANSI/AAMI/ISO 11137-1:2006/(R)2010, A1:2013-Sterilization of health care products-Radiation-Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices, ANSI/AAMI/ISO 11137-2:2013-Part 2: Establishing the sterilization dose and ANSI/AAMI/ISO 11137-2:2006(R)2010-Part 3: Guidance on dosimetric aspects.

LOAD EVALUATION AND QUALIFICATION TESTING

To develop a comprehensive sterility program, component bioburden load evaluation must first be performed. This requires the selection of individual components that represent the materials of construction, manufacturing location and manufacturing environment in which the finished single use product will be built. Equally important to component selection for bioburden load evaluation, is how the components will be tested. There are two common methods for component bioburden load evaluation: fluid path or submersion. Fluid path testing only subjects a components' internal fluid contact surface area, whereas submersion subjects a components' entire surface area for bioburden load evaluation. **CCG choose Submersion to determine the pre-sterilization average component bioburden level as it represents a more comprehensive approach for bioburden that has been introduced as part of the component manufacturing process.** Testing should be conducted by a qualified laboratory for bioburden load recovery qualification. The subsequent results of the testing will help define the components to be included in the final simulated product, which is often referred to as the "master device." In addition, dose mapping should be performed with the irradiator as part of qualification testing. Dose mapping ensures that the positions of dosimeters in the product pallet correctly read the gamma irradiation dose that the single use product received. For qualification testing, a 10^{-1} dosing level is used to demonstrate SAL 10^{-6}. This is demonstrated by proving at least 90% SAL 10^{-1}, which can be extrapolated to SAL 10^{-6} at regular dose rather than testing 1,000,000 simulated products. Upon dose mapping and exposure to 10^{-1} dosing level for the bioburden load associated with the simulated product, laboratory testing will determine if the single use product made in the cleanroom environment will successfully meet SAL 10^{-6}.

BARRIER QUALIFICATION

To ensure the single use product packaging maintains integrity of the sterile envelope, barrier qualification testing should be conducted. This involves testing post gamma irradiation, such as transportation simulation, gross leak testing, seal peel testing, accelerated aging and real time aging.

When conducting barrier qualification testing, it is important to consider the shelf life of the components that make up the simulated product. Component shelf life directly impacts the expiration date that can be assigned to a sterilized single use product upon successful barrier qualification testing. If the usable shelf life of a component in a single use product is shorter than 2 years, it would not be possible to assign a 2-year expiry to the sterilized single use product. To further extend the expiry of sterilized product, CCG has performed accelerated aging studies on components to increase their usable shelf-life and ensure the longest product expiry possible.

Sterile barrier qualification testing was performed in accordance with ANSI/AAMI/ISO 11607-1:2017 – Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems, and packaging systems and ASTM F1980–16 (2016) – Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

CCG's single use product packaging maintained its integrity after exposure to gamma-irradiation within the dose window (25kGy-45kGy), transportation simulation and three and one half (3.5) years of accelerated aging and therefore is deemed to be an acceptable sterile barrier system.

ROUTINE MONITORING, COMPONENT ADOPTION, AND IMPLEMENTATION

Maintaining a sterility program requires that simulated product is routinely subjected to the qualified sterilizing modality and tested for bioburden and sterility. The frequency of this testing is usually performed on a quarterly basis. When building simulated product for routine testing, it is important not to selectively pick "new" components, pull from special inventory that has been set aside or handle the components differently.

Rather, CCG's practice is to manufacture the product in a manner that is consistent to how any other single use product would be manufactured, so that the process is truly reflective. Furthermore, all components tested for bioburden that were not selected for inclusion in the simulated product are tested annually for bioburden to verify the levels remain consistent with initial test results.

With product innovation and dynamic user requirements, there may come a time when new components need to be adopted into a sterility program. A component may be added to a sterility program by testing for bioburden and assessing the results against the initial bioburden used to establish the sterility claim. It is best practice to perform this evaluation at regularly defined times to ensure that the simulated product on which the sterility claim is based remains a robust and accurate indicator of the assembly and environmental conditions under which the sterility claim was established. CCG is flexible in adopting new components to our sterility program when required for user requirements.

The startup and ongoing implementation of a sterility program is a constant cycle of assessment, monitoring and maintenance. Development of a successful program requires comprehensive qualification testing and routine monitoring. Continued adherence to governing standards and attentiveness in following best practices will provide biopharmaceutical manufacturers confidence that suppliers can deliver high quality sterilized single use products.

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