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⟨1229.14⟩ STERILIZATION CYCLE DEVELOPMENT

INTRODUCTION

The proper development and implementation of a sterilization process requires a number of important sequential steps to ensure that an appropriate sterilization process results in materials and products that are both microbiologically safe and suitable for their intended use.[1] Sterilization technologies that rely on heat, ionizing radiation, and chemicals often have the potential to alter the physicochemical properties of materials to which they are applied. In some cases, sterilization could either leave toxic residues on materials that were sterilized or result in impurities (i.e., leachables) being more readily released into products that contact them. Thus, it is necessary to consider sterilization not only as a means of eliminating microorganisms but also as a process that has the potential to change materials in a manner that impacts usefulness, safety, or both. A balance between the microbial lethality of a sterilization process and other aspects of patient safety must be established. A robust sterilization process that satisfies both is the desired objective of the cycle development activities.

PROCESS SCREENING

Radiation

The methods for establishment of radiation sterilization are described in detail in ISO 11137, and adherence to the most recent version of that standard is recommended.

Sterilizing Filtration

Filtration sterilization processes rely on exclusion of microorganisms and differ substantially from those that rely on lethality (see *Sterilizing Filtration of Liquids* ⟨1229.4⟩). Process development for filtration must consider many factors, such as adverse effects of the fluid on the filter (e.g., chemical compatibility) and of the filter on the fluid (e.g., extractables and leachables), as well as adsorption of fluid components. Physical interactions such as pressure differential, hydraulic shock, flow rate, temperature, and filtration capacity must also be considered. See ⟨1229.4⟩ for additional information.

Other Sterilization Methods

The first step in the development of a sterilization cycle is exposing the materials to the sterilization process and evaluating the impact that the process has on them. Initially, this determination can be a general screening process in which gross changes in appearance may be sufficient to confirm incompatibility. Where appearance is unchanged, the material should be evaluated for changes to its physical and chemical attributes. If the results are marginal, reductions in those parameters that most impact lethality and/or material effects may be beneficial. Tests conducted over a range of process lethality that would result in microbiological destruction should be performed. At this stage of development, the final process conditions required are not yet established, so flexibility in the preliminary evaluation is necessary. Common sense should be applied when considering sterilization process alternatives. For example, thermal treatments are inappropriate for refrigerated materials, items cannot be heated close to their melting point, sterilizing gases and liquids cannot penetrate sealed containers or nonporous materials, and other obvious restrictions may also be present. In the evaluation of items made of many materials (i.e., sealed vials, permeable pouches, etc.), consider the effect on all material components of the item being sterilized. Altering one or more components of the item may result in a favorable outcome. In many projects involving the sterilization of a custom-designed component, the sterilization process evaluation is an essential element of proof-of-principle studies. No component selection and manufacturing process design for a sterile material can be considered complete until a suitable sterilization process has been identified and fully evaluated, and renders the material sterile while having minimal effects on its physical and chemical attributes.

The following conditions are merely examples for consideration when evaluating materials for compatibility with the sterilization processes indicated:

1. Moist heat—at conditions sufficient to reliably kill the expected bioburden (see *Steam Sterilization by Direct Contact* ⟨1229.1⟩ and *Moist Heat Sterilization of Aqueous Liquids* ⟨1229.2⟩)
2. Dry heat—check for the lowest melting point of materials and process at 25° below the lowest melting temperature (see *Dry Heat Sterilization* ⟨1229.8⟩)
3. Liquids, gases, and vapors—at conditions sufficient to reliably kill the expected bioburden (see *Liquid-Phase Sterilization* ⟨1229.6⟩, *Gaseous Sterilization* ⟨1229.7⟩, and *Vapor Phase Sterilization* ⟨1229.11⟩)

Other conditions can be utilized in this preliminary evaluation, and multiple methods may need to be explored. Use information in the literature or provided by the suppliers to facilitate this effort. Materials should be changed if the initial materials are suspected of being incompatible with an otherwise acceptable method. The selected sterilization method should be the process that has the least impact on the

essential quality attributes of the material and delivers lethality sufficient to exceed the desired minimum probability of a nonsterile unit (PNSU).

BIOBURDEN EVALUATION

In parallel with the process described above, an assessment of the bioburden present in or on the items to be sterilized should be conducted (see *Monitoring of Bioburden* ⟨1229.3⟩). The initial evaluation should include an estimation of bioburden population and resistance. A control strategy for periodic bioburden monitoring for resistance and population should be instituted regardless of the results of the initial study (see ⟨1229.3⟩).[2] For radiation sterilization processes, the expectations for bioburden evaluation are established in ISO 11137.

Bioburden Resistance

For the remaining sterilization processes, the execution of a boil test (100° for 10 min) can serve as a basic screen for spore-forming microorganisms (see ⟨1229.2⟩). The absence of survivors in a boil test greatly simplifies the sterilization cycle development as the sterilizing conditions for non–spore-formers are less stressful on the production materials. If microorganisms are determined to survive the boil test, their resistance to the chosen sterilization process should be established. The boil test allows for estimation of a D value for a moist heat process. For other processes, a literature reference or laboratory study is required (see ISO 18472 *Sterilization of Health Care Products—Biological and Chemical Indicators—Test Equipment*).

Bioburden Population

If no microorganisms are recovered or only non–spore-formers are recovered, an estimation of bioburden population can be utilized to expedite selection of the appropriate process duration. As spore-forming bacteria are ubiquitous, the potential presence of spores in the bioburden should be given consideration.

ESTIMATION OF PROCESS DURATION

The minimum duration of the sterilization dwell period can be determined once the sterilizing method has been selected and the bioburden (as determined or assumed) information has been obtained. This is accomplished by rearranging *Equation 1*, used to estimate the PNSU (see *Sterilization of Compendial Articles* ⟨1229⟩).

$$\log N_U = \frac{-F}{D} + \log N_0 \qquad (1)$$

Rearrangement of the equation and solving for F results in *Equation 2*.

$$F = D(\log N_0 - \log N_U) \qquad (2)$$

N_U = assumed PNSU (NMT 1 positive unit in 10^6 units)

F = dwell time of the sterilization process at a defined condition expressed in minutes[3]

D = estimated D value of the bioburden in minutes

N_0 = estimated maximum population of the bioburden

The calculated F value represents the minimum duration of the process dwell period to reduce the assumed initial microbial population to less than the desired PNSU. Safety factors can be added to the assumed D value of the bioburden, the minimum desired PNSU, and the bioburden population estimate. The use of a safety factor reduces contamination risk as it increases the process duration, but it may adversely affect the materials being sterilized. With or without safety factors, determination of the estimated process duration under sterilizing conditions is a prerequisite to the subsequent activities.

Depending on the F value (or process dwell time) selected, the validation approach for sterilization can be determined. The preferred, but not required, method is the use of an overkill approach (see ⟨1229⟩) where the F value allows for complete inactivation of a resistant biological indicator. Where material limitations restrict the use of lengthy sterilizing conditions, the bioburden/biological indicator or bioburden methods may be more appropriate (see ⟨1229⟩).

FORMAL MATERIAL EVALUATION

Once the appropriate sterilization process has been chosen, the effects of that process on the materials should be reconfirmed (*1*). The requirements for this can vary from simple physical examinations for materials expected to be largely unaffected by the sterilization process, such as stainless steel or glass with steam, to comprehensive stability examinations for formulated products in their final container-closure configuration. The criteria for these studies should be objective wherever possible. It is useful to do a literature search for materials about which there is minimal experience, and to search and discuss potential material effects with suppliers. The preparation and sterilization of the test units for these formal studies can be conducted in a laboratory setting and must be fully documented.

When sterilizing using chemical agents, the sterilized materials should be tested for the presence of residual sterilant and its known degradation by-products. Post–sterilization cycle aeration or other treatments may be necessary to reduce these to acceptable levels.

BIOLOGICAL INDICATOR SELECTION

A biological indicator should be selected that is appropriate for the chosen sterilization process and its duration, as well as the intended validation approach (see *Biological Indicators for Sterilization* ⟨1229.5⟩). The chosen biological indicator provides a means to measure the

lethality of the process through the selection of biological indicator population and resistance. The sterilization process duration should not be adapted to accommodate the specifics of any biological indicator.

CONTAINER AND ITEM MAPPING

Studies should be performed to determine the location within the materials to be sterilized that is least likely to achieve sterilizing conditions. The mapping can be conducted using thermocouples, dosimeters, biological indicators, and/or chemical indicators placed within the materials. The materials to be sterilized should be wrapped or packaged and oriented as intended for routine use of the sterilization process. The wrapping and packaging materials and methods should be controlled to ensure reproducibility. It is essential when conducting these studies that the introduction of the measuring devices be accomplished in a manner that does not alter (positively or negatively) the penetration of the sterilant through any wrapping and packaging or through the material itself. If the materials to be sterilized have simple geometry, with minimal internal volume, and are sterilized with other more complex items, mapping of the simpler materials can be omitted. Interpolation of volume, density, dimension, and mass may be possible to reduce the extent of studies required. Mapping studies should be documented for future reference.

LOAD MAPPING

The initial use of a sterilization process should include confirmation that the sterilization conditions can be delivered throughout the entire load. Additional guidance on this, and the subsequent aspect of sterilization validation and process control, can be found in other chapters within the ⟨1229⟩ family of chapters.

REFERENCES

1. Association for the Advancement of Medical Instrumentation (AAMI). Compatibility of materials subject to sterilization. Arlington, VA: AAMI Technical Report No. 17; 2008.

[1] The term “materials”, as used throughout this chapter, includes drug substances, drug products, in-process materials, components, containers, closures, laboratory media, utensils, product contact materials, and other items subject to sterilization processes.

[2] Native bioburden must be routinely tested and trended with appropriate screening in place for organisms that may exceed the worst case in terms of population and/or survivability. If a more resistant organism and/or abnormally high population has been isolated through a screening procedure, the impact on the sterilization process to achieve the required sterility assurance level must be determined.

[3] The F value is equivalent to F_0 for moist heat, F_H for dry heat, or process dwell time L for other sterilization processes and is typically expressed in minutes.

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