Status: Currently Official on 12-Feb-2025
Official Date: Official as of 01-Nov-2019
Document Type: General Chapter
DocId: GUID-47A43122-C422-4E0B-BF92-3B408614555A_6_en-US
DOI: https://doi.org/10.31003/USPNF_M99941_06_01
DOI Ref: 99h5f

⟨1222⟩ TERMINALLY STERILIZED PHARMACEUTICAL PRODUCTS—PARAMETRIC RELEASE

Change to read:

INTRODUCTION

Parametric release is a practice to release finished product that relies on process control in lieu of end product testing to establish that a product is safe, pure, efficacious, and of suitable strength for commercial or clinical use. Parametric release is based on demonstrating that in-process conditions relevant to the establishment of key product quality attributes were attained and maintained throughout the relevant manufacturing steps. One attribute for which in-process controls would replace end product testing is sterility. The radiation sterilization of articles described in *Radiation Sterilization* ⟨1229.10⟩ performed in accordance with International Organization for Standardization (ISO) 11137 was the first sterilization process to use in-process controls and monitoring to replace sterility testing. The application of parametric release specifically to the attribute of sterility for commercial use requires prior regulatory approval.

Appropriately designed, validated, and controlled sterile product manufacturing systems are capable of exceptionally consistent performance in the preparation of products that have a probability of a nonsterile unit (PNSU) of $\leq 10^{-6}$. The exceptionally low probability of microbial presence in products manufactured using these systems renders the analytical methods described in *Sterility Tests* ⟨71⟩ statistically ineffectual.

While theoretically the limit of detection of the sterility tests is one viable cell, in actuality the limit of detection is likely far greater. A major limitation of ⟨71⟩ is that it is based on a limited sample. The probability of failing a sterility test given a contamination rate of 0.1% (an unacceptably high level of contamination) is 2% (where $n = 20$). For the contamination control capabilities achieved by well-controlled manufacturing systems, the probability of a sterility test detecting that level of contamination would likely be well below the limit of detection of the procedure. For these reasons, parametric release is the default mode of product release and should be used in lieu of sterility testing unless parametric release is not feasible.

In a parametric release program, sterility assurance is achieved by process, facility, and systems engineering; the establishment of appropriate risk-based user requirement specifications; and is conclusively demonstrated by the establishment, control, and monitoring of process parameters that confirm those user requirements are met. All modalities of sterile manufacturing should achieve ▲▲ (ERR 1-Nov-2019) a PNSU of $\leq 10^{-6}$. Parametric programs of product release should ensure all elements referenced in *Sterilization Assurance* ⟨1211⟩ consistently support the highest level of control.

Conditionally, terminal sterilization processes for the manufacture of products labeled sterile are candidates for parametric release. Terminal sterilization is the application of a suitable sterilization technology to a product, in its final sealed container or packaging, in a manner that achieves ▲▲ (ERR 1-Nov-2019) a PNSU of $\leq 10^{-6}$. Terminal sterilization may be conducted using any sterilization method that can be demonstrated to achieve a PNSU of $\leq 10^{-6}$ while at the same time retaining all other required product quality attributes. Examples of sterilization methods that have been successfully used to sterilize drug products or medical devices in their primary package are moist heat, dry heat, gas, and radiation. Processing parameters, critical processing parameters, and operational ranges ensuring the requisite microbial destruction should be understood, defined, measured, and controlled to support parametric release.

USER REQUIREMENTS

Establishing precise, clearly defined requirements that demonstrate in-process conditions are attained and maintained throughout the relevant manufacturing steps is essential for parametric release. Therefore, organizations wishing to develop and validate a candidate parametric release program must define the necessary user requirements specification (URS) and ensure that all conditions within that specification are met. Process control conditions and validation within the URS should be acceptable to relevant competent regulatory authorities.

The URS should include all critical functions of the technology, equipment, manufacturing process, environmental requirements, operational requirements, and other important characteristics necessary for ensuring provision of a sterile product. Since these requirements will be specific to the organization, the sterilization process utilized, the product and its intended use, the URS should be generated by the user.

In developing and validating a parametric release program, critical quality attributes and process parameters should be included in the URS:

Critical quality attributes: Criteria immediately before and after sterilization should be achieved to ensure that the sterility of every unit is sustained through expiry.

Process parameters: These should be accurate predictors of the assurance of product sterility. The operating ranges are developed based on the sterilization process, process capability, calibration tolerance limits, and process parameter criticality. Process parameters necessarily should be based upon a thorough process knowledge and understanding of risk. Control of critical process parameters within their validated operating ranges is necessary to assure the sterility of product manufactured within a parametric release program. Any failure to adequately control critical process parameters within the established, validated operating ranges will result in the disposal of the processed product.

Presterilization critical quality attributes and process parameters: Presterilization process parameters are important to ensure a consistent and minimized microbiological challenge to the sterilization process. For a parametric release program, the level of control of the environment and presterilization product intermediate bioburden (amount, frequency of recovery, and species) should be within validated ranges and ensure the efficacy of the subsequent sterilization. Recovery of species or forms of microorganisms that are generally recognized as representing an increased challenge to the sterilization process (e.g., spores for moist heat sterilization) should be infrequent as demonstrable by historical data. The sterilization process might not effectively control pyroburden (which is usually endotoxins). Therefore, pyroburden should be appropriately controlled throughout the manufacturing process. *Table 1* summarizes the minimum presterilization quality attributes and associated process parameters.

Table 1. Presterilization Critical Quality Attributes and Associated Process Parameters

Critical Quality Attributes	Process Parameters
Bioburden and the absence of specific microorganisms exhibiting an increased challenge to the mode of sterilization	• Pre-container-filling filter integrity[a] • Hold times (formulated product and filled product units)[a] • Cleaning and sterilization (where appropriate) of product contact surfaces[a] • Environmental and personnel control performance • Bioburden of excipient, raw material, drug substance, container, closure
Pyroburden	• Hold times (formulated product and filled product units)[a] • Cleaning and sterilization (where appropriate) of product contact surfaces[a] • Pyroburden of excipient, raw material, drug substance, container, closure
Filled container and closure integrity	• Filling and sealing control performance[a] • Container and closure component dimensions and material properties

[a] Critical process parameters.

Sterilization process parameters: Control of process parameters during the sterilization process is important to ensure a consistent and predictable level of product sterilization within the process' validated state. During the sterilization process, critical process parameters are monitored and recorded. Appropriate chemical, physical, or biological load monitors should be used to demonstrate lethality imparted upon the load. For example, the parametric release of most heat terminally sterilized products should use Class 5 indicators or, in certain circumstances, Class 3 (ISO 15882:2008) load monitors. Load monitors are located at specific locations in the load determined from development and qualification data to ensure each unit receives the required minimum sterilizing conditions. Certain container–closure configurations may possess sites that are less accessible to the physical or chemical agent used to terminally sterilize (e.g., the obscured interface between a container and its closure). In these circumstances, biological indicators and heat penetration probes (where applicable) should be placed at such locations during development and qualification studies to determine the required process parameters. For a parametric release program, the risk of human error should be minimized by use of electronic and automated systems to ensure the control of the sterilization cycle. In addition to qualified personnel, an automated electronic assessment of the sterilization cycle should assess the critical process parameters against the validated values. The assessment should be recorded and evaluated for the disposition of product. The following are examples of sterilization critical process parameters:

- Distribution (maximum, minimum, profile) of the physical or chemical agent throughout the entire cycle
- Time duration (minimum and maximum for any phases of the cycle)

Post-sterilization: If all presterilization critical quality attributes and sterilization process parameters are within their validated ranges, then all product units should be accepted as sterile. Failure to adequately control and measure critical process parameter data within the established, validated operating ranges of the sterilization process results in the disposal of the processed product. Under these circumstances, the application of a sterility test to ensure sterility is not permitted. Repeat sterilization of product from prior processing that failed to meet critical process parameters is only acceptable when supported with appropriate validations and regulatory approvals. Subsequent to processing, successfully sterilized product should be physically segregated from nonsterilized and nonsterile product. Facility and/or equipment design may ensure physical segregation. Furthermore, an electronic or automated system should be used to reduce or remove the potential for mix-up due to human error.

RISK ASSESSMENT

A well-designed parametric release process is superior because the sum aggregate of risks associated with elements of the program are lower compared to those of a non-parametric program reliant upon the sterility test. Therefore, a parametric release program is founded upon a thorough assessment, understanding, and management of risk. The multiple requisite elements of the program addressing engineering, process, procedural, and human factors require several assessments of risk to account for the different failure modalities and risk factors for severity and probability. All risk assessments should include the process parameters, critical process parameters, and the means of mitigating risks that may contribute to the failure to achieve critical quality attributes. These risk assessments are required to ensure that every product unit in every sterilization load within every manufactured batch achieves the required level of sterility assurance. For new products or sterilization processes, a risk assessment should be conducted during process development. For existing product or processes, the risk assessments should include historical data evaluation.

The following risk assessments are necessary to support a parametric release program:

Presterilization product bioburden: Assessing the potential risk of high bioburden or highly resistant microorganisms (e.g., spore formers), the means of enumeration and characterization, and opportunities for and modalities of product contamination. The risk assessment should additionally include other bioburden-related risks that may not be controlled by the sterilization process, such as pyrogens, and their potential to detrimentally alter the formulation chemistry of the product.

Loading patterns: Evaluating the positioning, stacking, and distribution of product units within the sterilizer load, including the potential for damage during the loading of each load and during the sterilization process. Include the risk of product units failing to achieve sterility due to the aforementioned factors.

Container and closure: The container and closure system is an important material attribute in which risk assessment should evaluate the risk of non-integrity before, during, and after sterilization. This includes secondary packaging and the potential for damage, and event-related or time-related loss of integrity which could potentially allow microbial ingress.

Sterilization cycle: Evaluating the controls, real-time measurement (including the number, type, and position of load monitors), data acquisition, data handling, automated and electronic systems of process control and monitoring.

Product segregation: Risk assessment of product after sterilization should evaluate the means of product management and reconciliation (manual or electronic) and the physical segregation (manual or automated) of sterilized product from presterilized and nonsterilized product.

REFERENCES

1. International Organization for Standardization. ISO 15882:2008: Sterilization of health care products—Chemical indicators—Guidance for selection, use and interpretation of results.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<1222> TERMINALLY STERILIZED PHARMACEUTICAL PRODUCTS--PARAMETRIC RELEASE	Leslie Furr Associate Scientific Liaison	GCM2022 General Chapters - Microbiology 2022

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 43(5)

Current DocID: GUID-47A43122-C422-4E0B-BF92-3B408614555A_6_en-US
DOI: https://doi.org/10.31003/USPNF_M99941_06_01
DOI ref: 99h5f