

Terminal Sterilization and Potential for Parametric Release

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US Pharmacopeia

Introduction

Sterility of a drug product, in the strictest sense, is defined as “complete absence of microorganisms in the product.” However, the test for sterility as described in the Pharmacopoeias [1], is not a test on which any strong reliance can be based for sterility assurance of the product. Due to limitations in testing [2], the test for sterility is not a suitable release test to verify that a product complies with its release specifications for sterility. On the contrary, it is primarily intended as a shelf life test. Hence, release of a sterile product should not solely rely on a sterility test. Release criteria should include the conditions under which a product was manufactured, critical parameters of sterilization processes, data about presterilization bioburden and environmental conditions of manufacturing and subsequent aseptic processing. The sterility assurance level (SAL) of each batch of drug product is defined in probabilistic terms, where the likelihood of a contaminated unit or article is acceptably remote (a 10^6 probability of nonsterility (PNS) or a maximum of 1 non-sterile unit in a total of 1 million units is considered to be the minimally acceptable PNS).

Terminal sterilization involves filling of formulation in primary packaging containers followed by thermal, ionizing, or chemical modes of sterilization. Terminally sterilized products are typically released on the basis of compliance with sterility test results and a review of the sterilization cycle records.

Terminally sterilized products represent the lowest risk category of sterile pharmaceutical products. Unlike products aseptically manufactured in a microbiologically controlled environment, terminally sterilized products are subjected to a sterilization process the microbiological lethality of which can be quantified.

When the mode of sterilization is very well understood and the physical parameters of processing are well defined, predictability, measurability, and the lethality of the cycle has been microbiologically validated, the release of terminally sterilized batches or lots of sterile products, *parametric release* [3,4], without having to perform the requirements under Sterility Tests [1] is a possibility. However, the *use of parametric release for sterilization processes requires prior FDA approval*.

This article contains an overview of the information in USP on terminal sterilization, and parametric release. *The reader is directed to the fact that references to USP-NF contain “official” text, while references to Pharmacopeial Forum (PF), contains “proposed” text.*

Parametric Release

Prior Regulatory Approval is required before parametric release

can be used to substitute for end-product testing, and this requires submission to relevant competent authorities. Parametric release is an operational alternative to routine release testing of samples taken from every finished batch to be tested according to release specifications.

A critical requirement or proof for the suitability of parametric product release required by the regulators would include well-supported scientific rationale for the terminal sterilization process and well-documented validation data to support assurance that any marketed sample of product will be sterile and would pass the requirements for sterility as found in the general chapter *Sterility Tests* [1]. The documentation should include evidence that supports

- the establishment of critical process parameters and operational ranges of all critical steps of the manufacturing (sterilization) process are validated
- the process is reliably controlled and in-process requirements chosen for approval/rejection are decided on the basis of acceptance criteria and verified during validation
- the relationship between a critical process parameter and a specific quality attribute is well established
- the relationship between end-product testing and process monitoring is defined and established
- clear, specified procedures are in place describing the reporting and actions to be taken

Modes of Terminal Sterilization [3]

The modes of sterilization commonly used for parametric release are moist heat, ethylene oxide, and ionizing radiation sterilization

Moist Heat Sterilization

The most commonly used technique for terminal sterilization is autoclaving, which makes use of saturated steam. Moist heat sterilization of pharmaceutical products includes several types of sterilizing environments and sterilizing media. “Saturated steam, hot water spray, and submerged hot water processes are all considered as moist heat sterilizing environments. Different processes may be used to sterilize products by moist heat, and they include batch-type sterilizers and continuous-type sterilizers” [3].

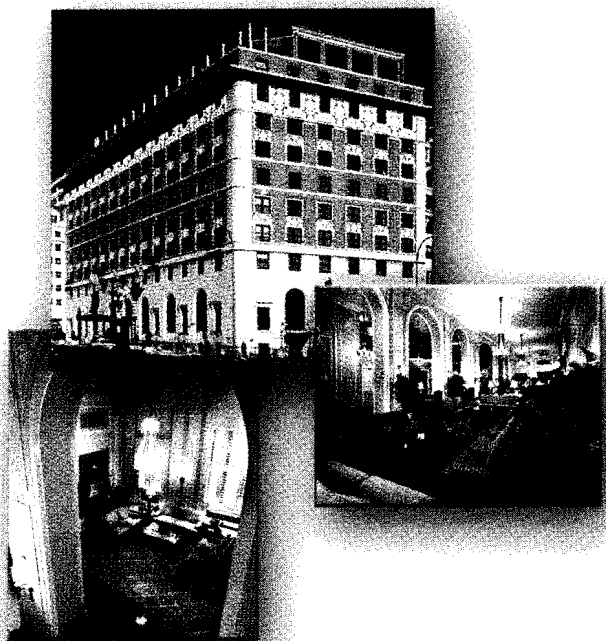
Ethylene Oxide Sterilization

“Sterilization by ethylene oxide (ETO) has more critical parameters than moist heat sterilization that are interrelated and that deter-

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mine whether, at a minimum, a 10^{-6} PNS is obtained when these parameters are within the specified limits of a validated cycle." [3]. Additionally, to ensure parametric release, biological indicators or physicochemical integrators can be used in each sterilized load.

Radiation Sterilization

Parametric (dosimetric) release of some pharmaceutical products has been accomplished through the use of radiation sterilizing processes: gamma and electron beam sterilization (i.e., ionizing radiation), either in the bulk or in their finished formats. Dosimetric release is provided by the use of a chemical dosimeter that measures the delivery of a minimum specified radiation dosage, which has been shown to provide sterilization of the product to a minimum 10^{-6} PNS.

Dosimetric release of a radiation-sterilized product depends on the delivery of at least a minimum dosage; thus, the critical operational parameters that govern the delivery of that dosage would include the stacking configuration within the radiation carrier, bulk density of the product, speed of the conveyor or carrier system, distance to the radiation source, duration of product exposure, and appropriate defined adjustments for a decaying radiation source. "Demonstration of consistency in the absorbed radiation dosage at areas of minimum and maximum zones of radiation absorption within the fully loaded carriers on a batch-to-batch basis is a necessary condition for dosimetric release of radiation-sterilized pharmaceutical products" [3].

Additional procedures used for terminal sterilization include blow-molding (at high temperatures), forms of moist heat other than saturated steam, UV irradiation, and vapor-phase hydrogen peroxide. The choice of the appropriate process for a given dosage form or component requires a high level of knowledge of sterilization techniques and information concerning any effects of the process on the material being sterilized.

Validation of Sterilization Process

Compliance of a terminally sterilized product with the 10^{-6} PNS requirement can be accomplished by several different sterilization cycle development approaches based on knowledge regarding the sterilization method selected for use with a specific product and their validation [3].

There are several different approaches taken to bring about terminal sterilization [5]. These include:

1. Bioburden-based processes
2. Biological indicator/bioburden combined processes
3. Overkill processes

A bioburden-based process requires extensive knowledge of product bioburden, and it is essential that at least a 10^{-6} PNS be attained after accounting for presterilization bioburden by the sterilization process. This means that if the product presterilization bioburden level is 10 colony-forming units (cfu) or one logarithm, at least seven logarithms of bioburden must be inactivated to assure a 10^{-6} PNS. This method requires the development of suitable critical control points within the process to control the bioburden titer. Consequently, products that readily permit bioburden survival require more controlled manufacturing environments and more precise in-process control. On the other hand, products that may be inherently antimicrobial or that can withstand more lethal sterilization processes will require correspondingly less rigorous control of the manufacturing process and less restrictive in-process control points. This process is better suited for cycle development for clean or ultra-clean products containing a consistently low level of CFU per product unit with a low frequency of spore-forming microorganisms. Also, this process may be necessary to permit terminal sterilization of a product that may potentially lose key

qualities or attributes as a result of a more rigorous sterilization process or the overkill approach.

When a sterilization process that demonstrates the inactivation of high numbers of biological indicator microorganisms known to be resistant to the *process is necessary, the biological indicator/bioburden combined process* is generally used in preference to utilizing an *overkill process*. This process requires knowledge of the bioburden load on and in the product and a database relative to the sterilization resistance of the bioburden. The relative resistance of the selected biological indicator to that of the bioburden must be established on or in the product. Frequently, biological indicator counts of approximately 10⁶ spores per indicator are used in the development of such processes. Fractional exposure cycles are generally conducted to determine the relative sterilization resistance (or D value) between product inoculated with the biological indicator microorganism(s) and frequently encountered bioburden. This process is frequently used for sterilization cycle development by manufacturers of terminally sterilized parenteral products and for ethylene oxide sterilization of medical devices.

The *overkill process* is commonly used when the article being sterilized is completely resistant to the sterilizing agent and sterilization cycle conditions without any concern for loss of product attributes or quality. When using this process, knowledge about product bioburden count data and the prevalence of spore formers is necessary to ensure that the materials are not adulterated before sterilization. The database for this process need not be as extensive as bioburden data required for the bioburden process or the biological indicator/bioburden process.

For compliance with the Code of Federal Regulations (CFR), Part 211 on Good Manufacturing Practices for Finished Pharmaceuticals in section 211.165, states: "There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms," an alternate laboratory control test for sterility is required for any batch load of a product that is parametrically released. This may be a biological indicator, which is included in each batch of product that is terminally sterilized [6] or a physico-chemical indicator or integrator [7].

Validation of most sterilization processes includes the validation of physical parameters of the process and of its microbiological effectiveness through the use of biological indicators because they provide a means of comparing physically measured lethality data with biological lethality.

The predictable effectiveness of bioburden-based terminal sterilization is based on the number and resistance of microorganisms on or in a product. Therefore, one component of parametric release is an active microbiology control program to monitor the count and sterilization resistance of product bioburden. Bioburden control and enumeration is of far less significance when the overkill process design is used. In many cases, overkill processes do not require extensive ongoing assessment of bioburden and require less in-process con-

trol of the manufacturing environment.

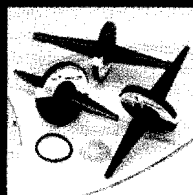
Sterilization Microbiology Control Program [3]

To ensure that the microbiological status of the product, prior to being terminally sterilized, has not significantly deviated from the established microbiological control level used for validation of the sterilization process, a control program is necessary.

The microbiology control program should include the monitoring of the bioburden on or in the product and the microbiological status of any necessary containers, closures, or packaging materials and

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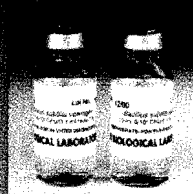
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the environment where the product is processed. The control program is particularly important in cases where the terminal sterilization is not based on overkill, but rather on the bioburden or combined bioburden/biological indicator cycle development approach.

Change Control System [3]

"Changes introduced to the sterilization processing equipment could result in a significant departure of the initially validated parametric release process. It is, therefore, essential that a change control system be instituted. A change control system is a formal system with appropriate standard operating procedures, would include assessment and approval of all the changes in relation to the critical parameters included in parametric release, including, technical and management review and "go-no go" hurdles. If a change would significantly affect any critical parameter, each parameter would have to be revalidated in terms of sterility assurance of the pharmaceutical product to a minimum 10⁻⁶ PNS. Appropriate regulatory notification would also be part of the revalidation process" [3].

Release Procedures [3]

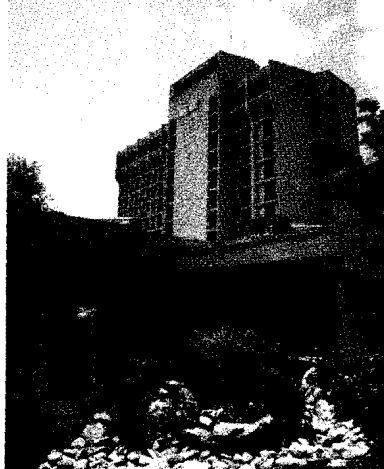
"A quality assurance program should be established that describes, in detail, the batch or lot release steps for parametric release of sterilized products and the required documentation. Although the assessment of the sterility assurance of products is primarily based on measurement of physical process parameters, a number of areas should be reviewed, documented, and approved for the parametric release of these products" [3]. These areas may include the following: a review of batch records; a review of the ongoing microbiological environmental control program results and pre-sterilization bioburden; and a review of records of thermographic data and results of indicators that may have been used to demonstrate process control. It is also

important to ensure that the sterilizer is current relative to calibration, maintenance, and revalidation.

"The implementation and practice of parametric release is not an intermittent program. Once such a program is implemented, release of the sterilized product is made in accordance with the requirements of the regulatory approved program. Product release by other means is not acceptable if the predefined critical operational parameters are not achieved" [3].

Summary

Release of a sterile product, due to limitations in testing, cannot solely rely on a pharmacopeial sterility test. To verify that a product complies with its release specifications for sterility (PNS /SAL), release criteria must include the conditions under which a product was manufactured, critical parameters of sterilization processes, data about presterilization bioburden and environmental conditions of manufacturing and subsequent aseptic processing. PNS of 10⁻⁶ can be achieved either by *terminal sterilization* or aseptic processing. *Terminal sterilization* involves filling of formulation in primary packaging containers followed by thermal, ionizing, or chemical modes of sterilization. Products which cannot withstand the rigors of terminal sterilization are aseptically processed. With *prior regulatory approval*, end-product sterility testing of terminally sterilized articles can be substituted by submission of well-supported scientific rationale for the terminal sterilization process and well-documented validation data to support assurance that any marketed sample of product will be sterile and would pass the requirements for sterility. This operational alternative to routine release testing of samples taken from every finished batch to be tested according to release specifications is called *parametric release*.



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