Technical Report No. 30 (Revised 2012)

Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat

2012

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PDA Task Force on Technical Report No. 30: Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat

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The content and views expressed in this technical report are the result of a consensus achieved by the authoring task force and are not necessarily views of the organizations they represent.

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1.0 Introduction

Parametric release is a sterility assurance release program that is founded upon effective control, monitoring, and documentation of a validated sterile product manufacturing process where sterility release is dependent upon demonstrated achievement of critical operational parameters in lieu of end product sterility testing. In this program, critical operational parameters and performance attributes are determined for process steps that occur prior to and during the performance of the sterilization process. The parametric release program is based on effective process control, monitoring, and documentation as well as a thorough understanding of the validated moist heat sterile product manufacturing process. A validated moist heat sterilization process must deliver a probability of a non-sterile unit (PNSU)[i] that is less than or equal to 10^{-6} for pharmaceutical and medical device products.[ii]

The previous version of *PDA Technical Report No. 30: Parametric Release of Pharmaceuticals Terminally Sterilized by Moist Heat* was published in 1999. Since 1999, many regulatory agencies and pharmacopoeial organizations across the globe have recognized the use parametric release and have fostered its implementation through the development of supporting standards, guidances and recommended practices. This growing adoption of parametric release necessitated an update to the 1999 report. This update provides current demonstrated best practices of this sterile product release method with an emphasis on use of science-based approaches during the development of a parametric release program for pharmaceutical and medical device products terminally sterilized by moist heat.

The sterility test has been widely used as the primary sterile product release criterion for moist heat sterilized pharmaceutical products and medical devices for many years. However, the sterility test is limited in its sensitivity and lacks statistical significance for the evaluation of sterility for terminally sterilized products given the exceedingly low probability of detection of contaminated units ***(1).*** The lack of statistical significance of the sterility test is summarized in **Appendix A** through a probability analysis of detecting sterility test positives with various contamination rates and sample sizes.

As a result of the limitations of the sterility test, the parametric release program has been developed as a proactive and science-based alternative to post-process (reactive) sterility testing for sterile product release. With parametric release, an acceptable sterility test cannot be used to support release for sterile products where one or more critical operational parameters have not been met.

The moist heat sterilization process is well-suited for the parametric release program because:

- it is well understood and dependable
- it is easily controlled and validated
- it is universally recognized for its effectiveness
- it delivers broad spectrum lethality (molds, yeasts, bacteria/spores, viruses)
- lethality can be mathematically modeled

The task force that participated in the development of this technical report was comprised of industry scientists, microbiologists and engineers from regions across the globe to ensure scientifically sound best practices were presented regarding parametric release of moist heat sterilized pharmaceutical products and medical devices.

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[i] Since Sterility Assurance Level (SAL) defines sterility in terms of probability of non-sterility, PNSU will be used in this report since *this term* accurately reflects this expression.

[ii] Although not acceptable for use with drugs, it is recognized that a PNSU of $\leq 10^{-3}$ is adequate in some regions for certain low risk medical devices (e.g., where intended use includes non-compromised tissue contact with devices such as gowns and towels).

This technical report underwent technical peer review that provided feedback from regulatory and industry professionals in the Americas, Asia-Pacific and Europe. The report should be considered a guide and is not intended to establish standards for parametric release.

1.1 Scope

This PDA technical report is intended to provide a single-source set of recommendations on developing a parametric release program that include demonstrated best practices that should be considered for development of a moist heat sterilization program. The report is built on the foundation of moist heat sterilization science presented in PDA Technical Report No. 1, which may be referred to for greater detail on the science of sterilization, sterilization cycle development and validation ***(2).***

Concepts provided in this report are applicable to pharmaceutical and biopharmaceutical products as well as combination products and medical devices (e.g., ophthalmic devices, nasal sprays) that are terminally sterilized with moist heat in support of parametric release programs. Due to the well-recognized limitations of the sterility test, the task force firmly believes that the practices and approaches endorsed by this technical report should also be considered for use with robust moist heat sterilization programs that employ the sterility test for release purposes. From a scientific perspective, the use of a sterility test for release purposes should not exempt a manufacturer from adopting state of the art best practice in the assurance of sterility.

This report is organized chronologically in order to facilitate development of a parametric release program. An overview of the elements of a sterilization program that provide the foundation for a parametric release program is provided. This overview is followed by discussion of process development that includes identification and classification of operating parameters upon which load release is based. Current thinking on maintaining the validated state through equipment qualification, process validation and ongoing process monitoring is then provided. Recommendations on the type of information that may be useful when submitting documentation for approval of a parametric release program are also included.

Since quality risk management is pivotal to the process control required for parametric release, an example risk assessment using a modified Failure Mode Effects Analysis (FMEA) assessment is provided in **Appendix B** with reference to sections addressing each assessment step.

This technical report also does not specifically address sterilization of microbiological media, sterilization of laboratory supplies or steam in place (SIP). The body of this report does not address all region-specific regulatory expectations, but provides current, science-based, best practices for use by industry and regulatory professionals. It is recommended that the authorities in the reader's region be consulted for current parametric release expectations.

A list of recommended supplemental reading references (**Section 9.0**) as well as references cited in this technical report (**Section 10.0**) provide additional information on the development of a parametric release program.