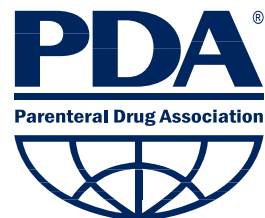


Technical Report No. 30 (Revised 2012)

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

2012



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

Authors

Mike Sadowski, Baxter Healthcare Corporation (Task Force Chair)

Marion Andersen, BS SM, Fresenius Medical Care

Tom Berger, Ph.D., Hospira, Inc. (Retired)

Steve Douglas, Hospira, Inc.

Julian Kay, GSK UK

Genevieve Lovitt-Wood, G.I. Lovitt & Associates

Terry Munson, Parexel Consulting

Ronald J. Nekula, Sr., Bayer HealthCare

Radhakrishna Tirumalai, Ph.D., USP

Bob Tomaselli, Johnson & Johnson

Contributors

James P. Agalloco, Agalloco & Associates

Rick Friedman, CDER, FDA

Thomas Genova, Ph.D., Johnson & Johnson

Andrew Hopkins, MHRA

David Jaworski, CDER, FDA

Russell Madsen, The Williamsburg Group

John Metcalfe, Ph.D., CDER, FDA

Steffen Prowe, Ph.D., Beuth University for Applied Sciences Berlin

Christopher Smalley, Ph.D., Merck & Co.

Marla Stevens-Riley, Ph.D., CDER, FDA

Kevin Trupp, Hospira, Inc. (Retired)

Brenda Uratani, Ph.D., CDER, FDA

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.

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

Technical Report No. 30 (Revised 2012)

© 2012 Parenteral Drug Association, Inc.
All rights reserved.



Table of Contents

<p>1.0 Introduction 1</p> <p style="padding-left: 20px;">1.1 Scope 2</p> <p>2.0 Glossary of Terms 3</p> <p>3.0 Parametric Release Program Elements 7</p> <p style="padding-left: 20px;">3.1 Quality Risk Management 7</p> <p style="padding-left: 20px;">3.2 Personnel 7</p> <p style="padding-left: 20px;">3.3 Product Design 7</p> <p style="padding-left: 20px;">3.4 Manufacturing Process Design 8</p> <p style="padding-left: 40px;">3.4.1 Product Bioburden Monitoring and Control 8</p> <p style="padding-left: 40px;">3.4.2 Product Segregation 9</p> <p style="padding-left: 40px;">3.4.3 Sterilization System Design (Equipment and Utilities) 10</p> <p style="padding-left: 40px;">3.4.4 Sterilization Process Considerations 11</p> <p style="padding-left: 20px;">3.5 Biological Indicator Certification 11</p> <p>4.0 Process Development 12</p> <p style="padding-left: 20px;">4.1 Load Definition 12</p> <p style="padding-left: 40px;">4.1.1 Load Pattern Development 12</p> <p style="padding-left: 20px;">4.2 Determination of Operational Parameters 12</p> <p>5.0 Equipment Qualification and Process Validation 14</p>	<p>6.0 Ongoing Process Monitoring And Control 15</p> <p style="padding-left: 20px;">6.1 Load Release 15</p> <p style="padding-left: 20px;">6.2 Change Control 15</p> <p style="padding-left: 20px;">6.3 Requalification and Revalidation 16</p> <p style="padding-left: 20px;">6.4 Planned Preventative Maintenance 16</p> <p>7.0 Submission Documentation 17</p> <p style="padding-left: 20px;">7.1 Risk Assessment Summary 17</p> <p style="padding-left: 20px;">7.2 Sterilization Process Description 17</p> <p style="padding-left: 20px;">7.3 Manufacturing Process Description 17</p> <p style="padding-left: 20px;">7.4 Sterilization Validation Summary 17</p> <p style="padding-left: 20px;">7.5 Sterile Product Release Procedure 17</p> <p style="padding-left: 20px;">7.6 Prior Manufacturing Experience for Risk Assessment 17</p> <p>8.0 Appendices 19</p> <p style="padding-left: 20px;">APPENDIX A: Significance of the Sterility Test 19</p> <p style="padding-left: 20px;">APPENDIX B: Risk Assessment for Adoption Of Parametric Release 20</p> <p>9.0 Supplemental Reading 25</p> <p>10.0 References 26</p>
--	--

FIGURES AND TABLES INDEX

<p>Table A-1 Probability Acceptance of Various Contamination Based on Sample Size..... 19</p> <p>Figure B-1 Example Liquid Product Sterilization Process Flow 21</p>	<p>Table B-1 Qualitative Risk Ranking Chart..... 22</p> <p>Table B-2 Risk Prioritization Ranking Chart 22</p> <p>Table B-3 FMEA Example 24</p>
--	---

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.

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).