# Technical Report No. 22 (Revised 2011) Process Simulation for Aseptically Filled Products


2011

## Process Simulation for Aseptically Filled Products PDA Task Force

**James Agalloco,** Agalloco & Associates, Inc. (Co-chair)

**Harold S. Baseman,** Valsource LLC (Co-chair)

**James E. Akers,** Ph.D., Akers Kennedy & Associates, Inc.

**Richard Boeh,** PQCA, LLC

**Don E. Elinski,** Lachman Consultant Services, Inc.

**Carol Lampe,** J.M. Hansen & Associates, Inc.

**Stephen E. Langille,** Ph.D., U.S. Food and Drug Administration

**Sandy Lowery,** Quality Systems Consulting, Inc.

**Russell E. Madsen,** The Williamsburg Group, LLC

**Gary B. McNassor,** Pfizer Inc.

**Gerry Morris,** Ph.D., Eli Lilly & Co.

**Anthony Pavell,** APP Pharmaceuticals

**Maureen Reagan Mueller,** Quality Systems Consulting, Inc.

# Process Simulation for Aseptically Filled Products

## Technical Report No. 22 (Revised 2011)

ISBN: 978-0-939459-35-3


# Table of Contents


**1.0 INTRODUCTION ..... 1**
- 1.1 Scope ..... 1
- 1.2 Previous PDA Publications ..... 1
- 1.3 Reason for Revision ..... 2
- 1.4 Purpose ..... 2

**2.0 GLOSSARY OF TERMS ..... 5**

**3.0 PROCESS SIMULATION CONCEPTS AND PRINCIPLES ..... 8**
- 3.1 Number and Frequency of Simulations ..... 8
- 3.2 Worst Case ..... 8
- 3.3 Risk Assessment ..... 9
- 3.4 Ongoing Evaluation ..... 9

**4.0 PROCESS SIMULATION FOR STERILE DOSAGE FORMS ..... 10**
- 4.1 Aseptic Compounding Activities ..... 10
- 4.2 Solutions ..... 11
- 4.3 Lyophilized Products ..... 11
  - 4.3.1 Simulated load/unload with Shortened Hold Time ..... 11
  - 4.3.2 Simulated lyophilization ..... 12
  - 4.3.3 Special Considerations unique to the Production of lyophilized Products ..... 12
    - 4.3.3.1 Freezing of Media ..... 12
    - 4.3.3.2 Vacuum levels and Duration ..... 12
    - 4.3.3.3 Anaerobic Conditions ..... 12
- 4.4 Suspensions ..... 13
- 4.5 Ointments/Creams/Emulsions/Gels ..... 13
- 4.6 Powders ..... 13
  - 4.6.1 Liquid Medium Filled by the Powder Filling Equipment ..... 14
  - 4.6.2 Dry Powder Filler with Supplementary Liquid Fill Capability ..... 14
  - 4.6.3 On-line liquid Fill Followed by on-line Powder Fill ..... 15
  - 4.6.4 On-Line Powder Fill Followed by on-line Media Fill ..... 15
  - 4.6.5 Special Considerations Unique to the Simulation of Aseptic Filling of Sterile Powders ..... 15
- 4.7 Other Dosage Forms and Device/Drug Combinations ..... 16
- 4.8 Other Aseptic Processing Technologies ..... 16
  - 4.8.1 Restricted Access barrier Systems ..... 16
  - 4.8.2 Form-Fill-Seal and blow-Fill-Seal ..... 16
  - 4.8.3 Isolation Technology ..... 16

**5.0 DOCUMENTATION ..... 18**
- 5.1 Process Definition ..... 18
- 5.2 Protocol/Procedure Preparation ..... 18
- 5.3 APS Execution Record ..... 19
- 5.4 Final Report ..... 20
- 5.5 Process Simulation Observation ..... 20

**6.0 MICROBIOLOGICAL ENVIRONMENTAL MONITORING ..... 21**

**7.0 ELEMENTS OF ASEPTIC PROCESS SIMULATIONS ..... 22**
- 7.1 Facility and Filling Machine Considerations . 22
- 7.2 Equipment Set-Up ..... 22
- 7.3 Media Selection and Preparation ..... 22
- 7.4 Inert Gassing ..... 22
- 7.5 Container Size ..... 23
- 7.6 Container/Closure Configuration ..... 23
- 7.7 Filling Speed ..... 23
- 7.8 Fill Volume ..... 23
- 7.9 Interventions ..... 24
- 7.10 Duration and Number of Units Filled ..... 24
- 7.11 Campaign operations ..... 26
- 7.12 Pre-Incubation Container Inspection ..... 26
- 7.13 Incubation Conditions ..... 27
- 7.14 Post-Incubation Inspection ..... 27
- 7.15 Unit Accountability and Reconciliation ..... 27
- 7.16 Growth Promotion ..... 27
- 7.17 Post Simulation Cleaning ..... 27

**8.0 INTERVENTIONS ..... 28**
- 8.1 Interventions ..... 28
- 8.2 Identifying Interventions Associated With an Aseptic Process ..... 28
  - 8.2.1 Inherent Interventions ..... 28
  - 8.2.2 Corrective Interventions ..... 28
- 8.3 Intervention Procedures ..... 29
- 8.4 Study Design ..... 29
- 8.5 Handling of Intervention-Related Containers .. 30

**9.0 PERSONNEL QUALIFICATION ..... 31**
- 9.1 Personnel Prerequisites ..... 31
- 9.2 Initial Qualification ..... 31
- 9.3 Periodic Qualification ..... 31
- 9.4 Access Without Prior Qualification ..... 31
- 9.5 Loss of Qualification Status ..... 31
- 9.6 Personnel Monitoring ..... 32

**10.0 ACCEPTANCE CRITERIA.....33**
10.1 Background ..... 33
10.2 Recommendations..... 33

**11.0 CONSIDERATIONS FOR INVESTIGATION.....34**

**12.0 ONGOING PROCESS EVALUATION.....35**

**13.0 APPENDICES .....37**
13.1 Selection and Sterilization of Placebo Powder/Materials ..... 37
13.2 Media Preparation and Sterilization..... 38
13.3 Aseptic Process Simulation Execution Sequence..... 39

**14.0 SUGGESTED READINGS .....41**

**15.0 REFERENCES .....42**

**FIGURES AND TABLES INDEX**

**Table 7.10.1** Duration and Number of Units Filled ..... 25

# 1.0 Introduction

This document replaces the original PDA *Technical Report No. 22, Process Simulation Testing for Aseptically Filled Products*, published in 1996. The intent of the current effort is to update that document to reflect the continuing changes that have occurred in aseptic processing technology within the global industry. We have attempted to address the subject as fully as possible recognizing the notable contributions by other organizations, regulators, compendia and individuals who have worked in this area. In addition the report provides guidance where risk based approaches may be applied.

This technical report was disseminated in draft for public review and comment prior to publication. Many of the submitted comments have been included in the final document. We believe this approach accomplished the widest possible review of the document and ensures its suitability as a valuable guide to industry in the area of process simulation for aseptic processing operations.

This technical report should be considered as a guide; it is not intended to establish any mandatory or implied standard. The reader must recognize that there may be additional requirements imposed because of new or localized regulatory expectations that are not included in this document. This technical report does not provide a universally appropriate template for the execution of process simulation studies. Each company must determine the appropriate rationale and approaches applicable to their unique operations.

A recurring theme in this report is the consideration of risk to product sterility and patient safety as criteria for the design of the aseptic process simulation studies. Regulatory authorities have issued recommendations for aseptic process study design and companies should be aware of these recommendations when planning their studies. However, the use of relative risk and scientific evaluation as a means to provide information used to make decisions on study design may be of benefit because it should result in better understanding of the aseptic process and its capabilities. The use of risk assessments and related information may result in studies which go beyond the recommendations of regulatory authorities. It may also result in studies which differ from those recommendations. However, it should not result in studies which are less effective than those recommended by regulatory authorities.

## 1.1 Scope

This technical report addresses process capability assessment for aseptic processing. Such assessments consist of one or more aseptic process simulations (APS) during pharmaceutical and biopharmaceutical formulation and filling activities (referred to as secondary manufacturing in many parts of the world). Aseptic operations required in the preparation of sterile bulk materials and biotechnology inoculums, and feed materials are not a part of this document; refer to PDA *Technical Report No. 28: Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals* ***(1)***.

While the focus of this document is on aseptic processing in the pharmaceutical and biopharmaceutical industry, application of the concepts and principles to the preparation of sterile medical devices and diagnostics may be appropriate.

## 1.2 Previous PDA Publications

PDA has published previous reports on the aseptic filling process: *Technical Monograph No. 2: Validation of Aseptic Filling for Solution Drug Products; Technical Report No. 6: Validation of Aseptic Drug Powder Filling Processes,* and the 1996 edition of this report, *Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products* ***(2–4)***.