

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

© 2011 Parenteral Drug Association, Inc.

All rights reserved.



Table of Contents

1.0 INTRODUCTION	1	5.0 DOCUMENTATION	18
1.1 Scope.....	1	5.1 Process Definition.....	18
1.2 Previous PDA Publications.....	1	5.2 Protocol/Procedure Preparation	18
1.3 Reason for Revision.....	2	5.3 APS Execution Record.....	19
1.4 Purpose	2	5.4 Final Report	20
2.0 GLOSSARY OF TERMS	5	5.5 Process Simulation Observation	20
3.0 PROCESS SIMULATION CONCEPTS AND PRINCIPLES	8	6.0 MICROBIOLOGICAL ENVIRONMENTAL MONITORING	21
3.1 Number and Frequency of Simulations.....	8	7.0 ELEMENTS OF ASEPTIC PROCESS SIMULATIONS	22
3.2 Worst Case.....	8	7.1 Facility and Filling Machine Considerations	22
3.3 Risk Assessment.....	9	7.2 Equipment Set-Up.....	22
3.4 Ongoing Evaluation.....	9	7.3 Media Selection and Preparation	22
4.0 PROCESS SIMULATION FOR STERILE DOSAGE FORMS	10	7.4 Inert Gassing	22
4.1 Aseptic Compounding Activities	10	7.5 Container Size.....	23
4.2 Solutions	11	7.6 Container/Closure Configuration	23
4.3 Lyophilized Products.....	11	7.7 Filling Speed	23
4.3.1 Simulated load/unload with Shortened Hold Time	11	7.8 Fill Volume	23
4.3.2 Simulated lyophilization	12	7.9 Interventions.....	24
4.3.3 Special Considerations unique to the Production of lyophilized Products	12	7.10 Duration and Number of Units Filled	24
4.3.3.1 Freezing of Media	12	7.11 Campaign operations.....	26
4.3.3.2 Vacuum levels and Duration	12	7.12 Pre-Incubation Container Inspection	26
4.3.3.3 Anaerobic Conditions	12	7.13 Incubation Conditions	27
4.4 Suspensions	13	7.14 Post-Incubation Inspection	27
4.5 Ointments/Creams/Emulsions/Gels	13	7.15 Unit Accountability and Reconciliation	27
4.6 Powders	13	7.16 Growth Promotion.....	27
4.6.1 Liquid Medium Filled by the Powder Filling Equipment.....	14	7.17 Post Simulation Cleaning	27
4.6.2 Dry Powder Filler with Supplementary Liquid Fill Capability	14	8.0 INTERVENTIONS	28
4.6.3 On-line liquid Fill Followed by on-line Powder Fill	15	8.1 Interventions	28
4.6.4 On-Line Powder Fill Followed by on-line Media Fill	15	8.2 Identifying Interventions Associated With an Aseptic Process.....	28
4.6.5 Special Considerations Unique to the Simulation of Aseptic Filling of Sterile Powders.....	15	8.2.1 Inherent Interventions	28
4.7 Other Dosage Forms and Device/Drug Combinations	16	8.2.2 Corrective Interventions	28
4.8 Other Aseptic Processing Technologies.....	16	8.3 Intervention Procedures.....	29
4.8.1 Restricted Access barrier Systems	16	8.4 Study Design	29
4.8.2 Form-Fill-Seal and blow-Fill-Seal	16	8.5 Handling of Intervention-Related Containers..	30
4.8.3 Isolation Technology.....	16	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	14.0 SUGGESTED READINGS	41
10.1 Background	33	15.0 REFERENCES	42
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	FIGURES AND TABLES INDEX	
13.2 Media Preparation and Sterilization.....	38		
13.3 Aseptic Process Simulation Execution Sequence.....	39	Table 7.10.1 Duration and Number of Units Filled	25