



Technical Report No. 77

The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology

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PDA The Manufacture of Sterile Pharmaceutical Products Using Blow-Fill-Seal Technology

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This technical report was developed and written in cooperation with the Blow-Fill-Seal International Operators Association (BFS IOA). The content and views expressed in this technical report are the result of a consensus achieved by the PDA authoring task force and are not necessarily views of the organizations they represent.

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ISPN 0-8-0-939459-94-0

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Table of Contents

1.0 INTRODUCTION	1	6.4 Sterility Assurance-related Critical Process Parameters	16
1.1 Purpose	1	6.4.1 Fill Nozzle Down Delay Timer.....	16
1.2 Scope	1	6.4.2 Bottle Blowing Timer.....	16
1.3 BFS Process Outline	1	6.4.3 Bottle Vent Timer.....	16
2.0 GLOSSARY OF TERMS	3	6.4.4 Master Fill Timer	16
2.1 Abbreviations	3	6.4.5 Individual Fill Timers.....	16
3.0 BFS EQUIPMENT	3	6.4.6 Fill Nozzle Up Delay Timer.....	16
3.1 Shuttle Type Machines (Open Parison Process).....	3	6.5 Implementation	16
3.2 Rotary Filling Machines (Closed Parison Process).....	4	6.6 Pre-process Preparation of Critical Areas	17
3.3 Additional Applications.....	5	6.6.1 Sanitization of Machine Surfaces	17
4.0 BENEFITS & SPECIAL CONSIDERATIONS OF BFS TECHNOLOGY	6	6.6.2 Cleaning of Product Contact Surfaces	17
4.1 Benefits.....	7	6.6.3 Sterilization of Product Pathway.....	18
4.2 Special Considerations	7	6.7 Product Validation	18
5.0 DESIGN	8	6.7.1 Container Closure Integrity Testing.....	18
5.1 Product Design.....	8	6.7.2 Leak Detection.....	19
5.1.1 Aseptic Processing versus Terminal Sterilization.....	8	6.7.3 Campaign Fill/Holding Time	19
5.1.2 Terminal Sterilization.....	8	6.7.4 In-Process Sampling	19
5.1.3 Polymer	9	6.8 Equipment Validation	19
5.1.4 Product Applications	9	6.8.1 Critical Zone Control	19
5.1.5 Container Design	10	6.8.2 Air Shower Design (Open Parison Machines)	20
5.1.6 Secondary Packaging	11	6.8.3 BFS Machine Room Environment	20
5.2 Equipment Design	10	6.8.4 Filtration Configuration	20
5.2.1 General	10	6.8.5 Filter Integrity	20
5.2.2 Product Pathway	11	6.8.6 Air/Gas Filtration.....	20
5.2.3 Mold Design	11	6.8.7 Aseptic Compounding and Other Pre-BFS Product Sterilization Approaches	21
5.2.4 Vacuum System	11	6.8.8 Environmental Monitoring.....	21
5.2.5 Deflashing.....	12	6.8.8.1 BFS Shuttle Machines	21
5.2.6 Equipment Monitoring	12	6.8.8.2 BFS Rotary Machines.....	22
5.3 Facility Design.....	12	6.8.9 Extrusion Considerations	22
5.3.1 Aseptic Processing Area	12	6.8.10 Controls	22
5.3.2 Polymer Storage and Distribution	12	6.8.11 Downstream Process	22
5.3.3 Utilities.....	13	6.9 Process Simulation (Media Fill) for Aseptic Filling Lines.....	22
6.0 OPERATIONAL AND QUALIFICATION CONSIDERATIONS	13	6.9.1 Design	22
6.1 BFS Process Validation and Advanced Technology	13	6.9.2 Interventions	23
6.2 Evaluating Critical BFS Process Parameters for Quality and Sterility.....	14	6.10 Gowning.....	24
6.3 Quality Attribute Critical Process Parameters.....	15	6.11 Facility Validation.....	24
6.3.1 Air Flow Rate.....	15	7.0 QUALITY RISK ASSESSMENT	24
6.3.2 Main Mold Vacuum Delay Timer.....	15	7.1 Product Contamination	25
6.3.3 Bottle Blowing Timer.....	15	8.0 REFERENCES	26
6.3.4 Seal Mold Vacuum Delay Timer.....	16	9.0 APPENDIX I: EXAMPLE OF A QUALITY RISK ASSESSMENT	28
		10.0 APPENDIX II: ENVIRONMENTAL PARTICLE MONITORING LEVELS	32

FIGURES AND TABLES INDEX

Figure 3.1-1	Diagrammatic Representation of the Open Parison BFS Process.....	4	Table 9.0-1	Severity Scoring Criteria	28
Figure 3.2-1	Rotary BFS Machine Schematic	5	Table 9.0-2	Probability of Occurrence Scoring Criteria	28
Figure 3.2-2	BFS Process Detail for Rotary Machines.....	6	Table 9.0-3	Likelihood of Detection Scoring Criteria	28
Table 5.1.3-1	Parameters for Assessing Polymer Selection.....	9	Table 9.0-4	Risk Decision Matrix	29
Table 5.1.5-1	Container Design Considerations	10	Table 9.0-5	Risk Priority Matrix 1 – Severity × Occurrence	29
Figure 6.2-1	Sterility-related Process Parameters during BFS Operations	15	Table 9.0-6	Risk Priority Matrix 2 – Severity × Occurrence × Detection	29
Table 6.5-1	Machine Parameter Test Sheet Example.....	17	Table 9.0-7	Quality Risk Assessment Report Example.....	30
Table 7.2-1	Examples of Contamination Risk Types Related to Operation	25	Table 10.0-1	Air Classifications and Prescribed Environmental Particle Levels	32
Table 7.2-2	Equipment-related Sources of Contamination	26			

1.0 Introduction

Blow-Fill-Seal (BFS) technology is the integration of plastic blow molding and aseptic filling on a single machine. The technology has been used in manufacturing liquid pharmaceutical product since the 1960s. The final container is created within the machine just prior to aseptic filling and hermetically sealed immediately after filling in one continuous, automated operation. It provides a unique combination of flexibility in packaging design and enhanced sterility assurance and has been accepted worldwide for both aseptic and terminally sterilized liquid products. BFS technology is currently used in more than 50 countries (1–4).

Considered “advanced aseptic processing,” BFS technology provides advantages over conventional filling when designing controls for the processes. The advanced aseptic processing designation is supported by various experiments that challenged BFS systems through contamination loading of both the surrounding environment and plastic components (5).

BFS processing offers a number of other advantages as well. It supports a simplified supply chain, which can result in a level of quality and control of primary packaging materials (i.e., resin only) that is not practical in pre-formed (glass, plastic, etc.) vial/stopper filling. And due to the rapid cool-down following container formation, biological and protein-based products can be safely processed in BFS machines. The equipment supports single-dose container packaging with flexibility for frequent changeover if short production runs are desired. BFS processing is also capable of incorporating pre-molded and pre-sterilized components (inserts) in the basic container, such as silicone stoppers for parenteral applications and injection-molded tip/cap inserts for metered drop control in multi-dose eye drop containers.

1.1 Purpose

The objective of this technical report is to provide recommendations specific to the operation of BFS technology for the manufacture of sterile pharmaceuticals (e.g., ophthalmics, parenteral, and inhalation). The intent is to provide supplemental information to assist the user with interpretation of international standards and regulatory guidance from the perspective of BFS operations. Consideration is given to specific aspects of BFS operations not covered in published information.

1.2 Scope

This technical report addresses considerations for BFS technology related to the installation and operation of the machinery and evaluation of related materials and final product containers. Support areas, such as laboratory, solution compounding, gowning airlocks, etc., are not considered specific to BFS and are not included within the scope of this document. This technical report is intended as a guide for the pharmaceutical industry and is not meant to supplement or duplicate any existing regulatory guidance. The content and views expressed in this technical report are the result of a consensus achieved by the members of the authorizing Task Force and are not necessarily the views of the organizations they represent.

1.3 BFS Process Outline

BFS technology is a pharmaceutical primary packaging-filling process that combines three operations (container formation, filling, and closure) that are typically performed separately in conventional filling operations. BFS containers are formed from an extruded thermoplastic parison, filled with product, and then sealed in a continuous, integrated, highly automated operation. Originally developed for use in other industries, BFS technology has been adapted for use in the manufacture of sterile pharmaceutical, medical device, biological, and veterinary products. The two most common types of BFS machines are the shuttling machine (open or cut parison) and the rotary machine (closed parison), which are both considered in this document. All steps of the BFS process are conducted under highly classified conditions per current regulatory standards (1,2).

In BFS processes, a thermoplastic polymer is used to form the primary container. Granulated polymer (plastic pellets) is supplied by a closed pathway via vacuum transfer. The system feeds polymer pellets into a standard plastic hot melt extrusion process. In the extrusion process, the polymer is heated to temperatures in excess of 170°C and subjected to pressures over 20,000 kPa (200 bar).