PDA
Parenteral Drug Association

Technical Report No. 77

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

www.pda.org/bookstore

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

Authors

Martin Haerer, Holopack Verpackungstechnik, Team Co-leader (BFS IOA)

Kenneth Muhvich, Micro-Reliance, LLC, Team Co-leader (PDA)

Peter Åkerman, AstraZeneca

Jaime Blanco, Genentech

Nermin Cehajic, KemPharm, Inc.

Kevin Downey, Teva Pharmaceutical

Ty Duginske, Baxter

Andrew Goll, Weiler Engineering, Inc.

Tim Kram, Rommelag USA, Inc.

Stacey Largent, Merck

Jesper Laursen, MELITEK A/S

Matt Payne, Ritedose Corporation

Patrick Poisson, United Therapeutics

Chuck Reed, Reeds and Rushes, LLC

Otto Schubert, Maropack AG

Jerry Webb, Nephron Pharmaceutical Corporation

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.

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

Technical Report No. 77

ISBN: 978-0-939459-94-0

www.pda.org/bookstore

Table of Contents

FIGURES AND TABLES INDEX

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., ophthalmic, 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 supplant 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).

The temperature, pressure, and encapsulation within the plastic in the extruder reduce the probability that any contaminants (such as particulates, fungal and bacterial endospores, and endotoxins) may come in contact with the final filled product ***(6).***

The plastic polymer is extruded into one or more continuous plastic tubes called parisons. Sterile filtered air or other gases are supplied through the extruder head at sufficient pressure to prevent the parisons from collapsing. The BFS process uses one of two mechanical methods to form the container(s): **1)** vacuum on the mold only; or **2)** a blowing process in combination with vacuum on the mold. Vacuum is employed with both methods to remove air around the container to aid in container formation. Containers larger than 30 mL typically require the addition of blowing with sterile air to complete the container formation.

During operations, the liquid formulation is supplied to the BFS system through a closed, sterile product pathway. The product pathway in BFS is an inherently safe design. It is completely closed and all product-contact surfaces, including the tank, hoses, filter housings, fill system, and filters (if provided, based on product specifications) are typically cleaned and sterilized in place before production begins.

The most common dosing mechanism is time pressure dosing (TPD). Other acceptable dosing systems include pumps and positive displacement systems. Upon completion of the dosing step, the top portion of the mold either closes (shuttle style) or rotates into compression (rotary style) to seal the container(s) and complete the BFS process.

The range of products that can be filled using BFS technology includes solutions, emulsions, suspensions, and low and high viscosity products, such as gels, creams, and ointments.

Typical solutions can be processed with integrated sterile filtration. Suspensions, emulsions, and highly viscous products can be processed with recirculation and without terminal filtration where a bulk sterilization process is implemented. In addition, BFS containers can be terminally sterilized by steam and other methods when required. Certain large molecule products cannot be sterile filtered or terminally sterilized, however, thus aseptic transfer of the product to the BFS machine is required.

BFS machine output (containers per hour) is dependent upon product and polymer physical characteristics, and container design. The number of containers produced per cycle is only limited by the number of containers that can be formed by the mold. The cycle time is dependent upon the product filling characteristics (e.g., viscosity, foaming) and the resin-dependent formation time required in mold.

