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

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.

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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).