BFS International Operators Association

The Manufacture of Sterile Pharmaceuticals and Liquid Medical Devices Using **Blow-Fill-Seal Technology**

Points to Consider







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Contents

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The BFS process is a technical one and appropriate and adequately trained expert personnel must be employed at each stage of the BFS process.

1. INTRODUCTION

Blow-Fill-Seal (BFS) technology has been used for pharmaceutical and liquid medical device manufacturing since the 1970s. This processing technology has become accepted worldwide for both aseptic and terminally sterilised liquid products and is currently used in more than 50 countries throughout the world.

BFS technology lacks harmonisation and specific standards on a worldwide basis. As a result, the technology has developed in an isolated fashion, with each company and each regulatory agency establishing its own interpretation of acceptable BFS practice.

In 1989, the Pharmaceutical Blow-Fill-Seal International Operators Association (BFS IOA) was established as an interest group of pharmaceutical and associated companies actively involved with BFS processing. The Association was formed to provide its members with an opportunity to exchange ideas and opinions, and to formulate agreement on operating standards. It also provides a forum to speak with a unified voice to machine manufacturers, commercial suppliers, and regulatory bodies. The Association has expanded worldwide and now has over 60 member companies.

In an attempt to establish a common understanding of acceptable practice in BFS processing, the Association first published a "Points to Consider for Pharmaceutical Blow-Fill-Seal Manufacturing Operations" (PTC) document in September 1993. The document addressed points specific to BFS processing but also covered many more general areas. The current PTC document focuses on issues specific or unique to BFS technology and has undergone periodic review and systematic updates since its inception.

This document is the culmination of several reviews during 2010 and 2011 and the most current version is from March 2012.

2. OBJECTIVE

The objective of the 'Points to Consider' document is to provide recommendations specific to the operation of Blow-Fill-Seal technology for the manufacture of sterile pharmaceuticals and liquid medical devices. The principles of BFS technology as applied to filling are considered to be the same in terms of machine process for both aseptically filled and terminally sterilised products.

This document provides information to supplement and to assist with interpretation of international standards and regulatory guidance from the perspective of BFS operations, and considers specific aspects of BFS operation which are not covered by existing published information.

The PTC is intended as a guide for industry and is not meant to supplant or duplicate any existing regulatory guidance. A list of current regulatory guidance references is provided in the Appendix.

- Equipment monitoring (process alarms)
- Blowing/ballooning air/inert gas requirements
- Exhaust system(s) (e.g. air removal from container during filling, removal of particles during knife cutting)
- Mould design
- Utilities (cooling, vacuum)
- Polymer feed system
- Deflashing system
  - It is possible to locate outside the cleanroom which will reduce particle generation in the cleanroom and to afford easy access

5.2.2 Control of critical zone environment

Traditionally, the critical zone in a BFS machine has been considered to be the point of fill protected directly by a sterile air shower. However, any area in which product or unsealed containers are exposed should be considered as the critical processing zone [2]. Normally, modern BFS machines should include protection around the shuttling zone of open parison machines.

FDA Guidance on aseptic operation of BFS machines recommends that *"Air in the critical area should meet Class 100 microbiological standards during operations"* and states that *"A well-designed BFS system should also normally achieve Class 100 (ISO 4.8) airborne particle levels" [3]*.

Current EU guidance refers to an "effective Grade A air shower", but does not define the area over which it is effective, the point of fill or the critical zone [1].

Note

EU GMP Annex 1 defines

- "at rest" as the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present and

- "in operation" as the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

BFS IOA suggests the following clarification of the definition for BFS processes

- "At rest": BFS machine, line with conveyor belts at rest, but with air shower and room ventilation in operation. Extruder (heated, not running) and mould carriage in standby. No operating personnel present.
- "In operation": BFS machine, line fully operational and filling, with the number of operating personnel present as allowed during normal running conditions.

5.2.3 Air shower design (shuttle type machines)

Localised ISO Class 4.8 conditions at the point of fill are provided by appropriate air shower design. The purpose of the air shower is to ensure that there is a continuous flow of sterile air of appropriate quality over the filling needles and point of fill. This air is either sterilised through sterilising grade cartridge filters or provided via HEPA filters.

Provision for ensuring that Class 4.8 conditions for viable particulates are met should be considered (see section 5.3.1).

Sterilisation or sanitisation of the surfaces of the air shower system downstream of the filter should be considered.

Methods for monitoring viable and non-viable during operation and rest in the air shower should be considered.

Alarm conditions for particulate levels should be considered with both alert and action points.

The effective operation of the air shower should be monitored continuously. Failure of the air shower should be alarmed.