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RESEARCH

Current Practice in the Operation and Validation of Aseptic Blow-Fill-Seal Processes

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ABSTRACT: In order to illustrate current practice in aseptic blow-fill-seal (BFS) technology, a worldwide survey was performed by the BFS International Operators Association. The results are summarized and compared to the media fill data from the Product Quality and Research Institute (PQRI) survey reported in 2003. The survey highlights the differences and shows the robustness of the BFS technology. Compared to the results from the PQRI survey, the BFS survey shows a tenfold lower frequency of contaminated media fills.

KEYWORDS: Aseptic production, Blow-fill-seal, Media fills

Introduction

The validation of aseptic processes using advanced processing techniques such as blow-fill-seal (BFS) technology continues to be an area of interest to pharmaceutical industry and regulatory authorities. To illustrate current industry practices with regard to aseptic processing using BFS technology, a survey was conducted by the Pharmaceutical Blow-Fill-Seal International Operators Association (BFS IOA; the BFS IOA was formed in 1987 to provide a forum for technical discussion on aspects of operation of BFS technology within healthcare manufacturing). The questionnaire used in this investigation was based on another industry survey, made in 2003, of 45 manufacturers who used aseptic processing (1). The original survey was conducted by the Product Quality and Research Institute (PQRI), and the questions in this BFS survey follow very closely those used by the PQRI. Questionnaires were sent to BFS users of aseptic processing worldwide.

Over a period of two years, 14 responses representing 90 filling lines in Europe, Australia, Asia, and America were received. This is significantly more BFS data than in a previously published aseptic survey made in 2001 (2). The purpose of this paper is to enlighten the differences between advanced BFS technology and conventional aseptic filling in vials and ampoules.

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Blow-Fill-Seal (BFS) Aseptic Processing

Aseptic processing using BFS technology forms (or "blows"), fills, and seals the pharmaceutical container in one unit operation. When appropriately configured the process may be regarded as an advanced aseptic process, as human intervention is minimized during the filling (3). A short description of the basic process steps is given below.

BFS technology uses plastic granules, typically low-density polyethylene (PE) or poly(propylene-co-ethylene) (PP/PE), as primary packaging raw material. The plastic granules are fed through a rotating extruder screw where friction is generated and, together with heat from heater bands, a homogenous melt is obtained. This melt is extruded through a circular orifice, producing a continuous tube of molten plastic. This is called a parison. A stream of sterile, filtered air keeps the open-ended parison inflated.

A mould moves to enclose the parison and a container is formed by either vacuum within the mould or blowing air to shape the polymer to the mould. As the container is formed the parison is cut.

To fill the formed container, the mould is moved or shuttled under the filling station, a transverse shift usually taking 1–2 seconds. Filling takes place under a constant stream of sterile, filtered air; after filling, the upper part of the mould is closed to seal the container. The process steps are outlined in Fig 1.

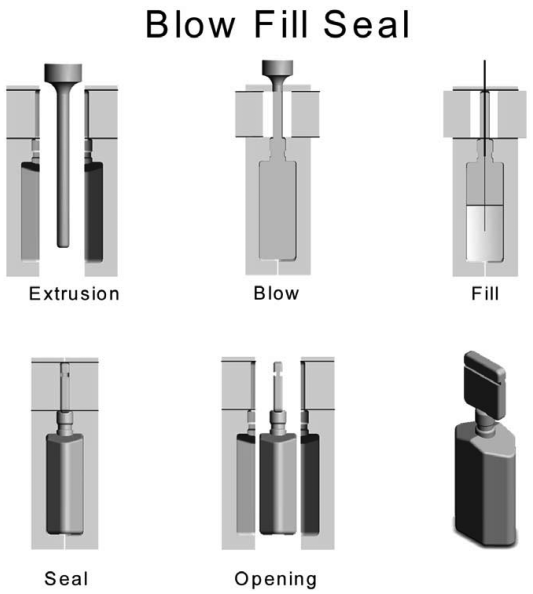

Figure 1

Schematic representation of the Blow-fill-seal process (parison cutting and shuttling takes place between the blow and fill stages)

In an alternative machine design, the plastic parison remains uncut, and filling needles are situated within the continuously extruded parison.

In most applications no aseptic connections are required. Clean-in-place and steam-in-place (CIP and SIP) systems ensure the entire aseptic system is sterile before production. Leak detection systems (100% in-process) are often installed downstream to exclude possible leaking units.

For aseptic processing it is generally required that filling machines are located in clean rooms constructed to meet ISO class 7 or 8 with a critical zone meeting Class 100/ISO class 5 microbiological standards under operational conditions (4–7).

BFS Industry Survey

The data were collected during the years 2003–2004 from 90 aseptic filling lines. Excerpts from the responses are presented below.

Filling environment

Cleanliness Class

All filling lines reported a cleanliness classification in the air shroud/shower of ISO class 5 (EU grade A).

The most common background cleanliness was ISO class 8 (EU grade C, in operation), followed by ISO class 7 (EU grade B, in operation).

Type of Filled Container

The type of containers filled on the 90 filling lines were

- Ampoules on 76 lines
- Units with aseptic inserts on six lines
- Large Volume Parenterals (LVP) on four lines
- Other single-dose units on four lines.

Filling Lines

As a first step, companies taking part in this survey were asked to list all aseptic BFS filling lines at their facility or facilities and fill out a rows in a spreadsheet for each media fill run performed in the past 12–14 month period.

Line Speed

TABLE I
Reported Average Number of Units Filled per Hour

Average Number of Units Filled per Hour	Number of Filling Lines	%
<2000	17	18.9
2001–5000	45	50.0
5001–10,000	18	20.0
>10,000	10	11.1

Comment: The most common line speed is in the range of 2000–10,000 units per hour. Line speed is dependent on fill volume and container size.

Batch Size

TABLE II
Average Number of Units Filled in a Batch

Average Number of Units Filled in a Batch	Number of Filling Lines	%
<5000	8	8.9
5001–10,000	3	3.3
10,001–100,000	23	25.6
100,001–1,000,000	48	53.3
>1,000,000	8	8.9

Comment: There appears to be a high frequency of batches with an average batch size above 100,000 units. This reflects the common use of BFS technology for filling small-volume products in relatively large batches.

Minimum and Maximum Volumes

TABLE III
Minimum Fill Volume Run on the Line (Specified in Milliliters per Container)

Minimum Fill Volume in Milliliters	Number of Filling Lines	%
<1	23	25.6
1–5	23	25.6
5.1–10	29	32.2
11–100	12	13.3
>100	3	3.3

TABLE IV
Maximum Fill Volume Run on the Line (Specified in Milliliters per Container)

Maximum Fill Volume in Milliliters	Number of Filling Lines	%
<1	7	7.8
1–5	27	30.0
5.1–10	18	20.0
11–100	30	33.3
>100	8	8.9

Comment: Only approximately 17% of the lines had a minimum fill volume of more than 10 mL, whereas approximately 42% of the lines had a maximum fill volume of more than 10 mL.

Duration of Fill in a Batch

TABLE V
Duration of the Longest Aseptic Processing Operation (Batch) in Hours (Includes Time at which Aseptic Transfers and Filling Begins to the Final Unit Filled)

Longest Aseptic Processing Operation in Hours	Number of Filling Lines	%
<10	3	3.3
11–50	27	30.0
51–100	36	40.0
101–200	24	26.7
>200	—	

Comment: A significant percentage of BFS aseptic operations takes place over extended filling times, i.e., longer than 12 h.

Media Fill-Specific Information

Number of Media Fills

Fourteen companies with a total of 90 filling lines performed 239 media fills during a 12–24 month period in 2003–2004.

Media Fill Batch Size

TABLE VI
Number of Media Units Filled and Number of Process Simulations

Number of Media Units Filled per Batch	Number of Media Fill Batch	%
<3000	2	0.8
3001–10,000	88	36.8
10,001–50,000	96	40.1
50,001–100,000	50	21.0
>100,000	3	1.3

Comment: More than 60% of the media fills had a batch size over 10,000 units.

TABLE VII
Excerpts from the PQRI Survey: Number of Media Units Filled and Number of Process Simulations

Number of Media Units Filled per Batch	Percentage of Media Fill Batches
<5000	23
5001–10,000	38
10,001–20,000	28
>20,000	11

Comment: The total number of media fills was 239 batches in the BFS study. The percentage of media fill batches with 10,000 or more filled units was significantly higher (62.4%) than the percentage reported in the PQRI study (39%).

Number of Contaminated Media Fills

Duration of a Typical Media Fill

TABLE VIII
Reported Duration of the Media Fill in Hours

Duration of Media Fills in Hours	Number of Media Fill Batches	%
<2	38	15.9
2–5	78	32.6
5–10	8	3.3
10–50	71	29.7
>50	44	18.4

Comment: The duration of media fills was more than 10 h for 57% of the batches in the BFS study.

TABLE IX
Reported Number and Percentage of Contaminated Media Fills (BFS and PQRI Surveys)

BFS Survey			PQRI Survey		
Total Number of Media Fill Batches	Number of Contaminated Media Fill Batches	Percentage of Media Fill Batches Contaminated	Total Number of Media Fill Batches	Number of Contaminated Media Fill Batches	Percentage Contaminated Media Fill Batches
239	2	0.837	606	54	8.91

Comments: Breakdown of contaminated media fills in the BFS survey (two of 239 runs contaminated):
- 1 unit out of 15,160, for a 0.0066% contamination rate
- 1 out unit of 51,200, for a 0.0019% contamination rate

Breakdown of Contaminated Media Fills in the PQRI survey (54 of 606 runs contaminated):
- 36 media fills had 1 contaminated unit
- 3 media fills had 2 contaminated units
- 4 media fills had 3 contaminated units
- 8 media fills had 4 contaminated units
- 2 media fills had 5 contaminated units
- 1 media fill had 1200 contaminated units

Discussion

The results of this survey represent the current status of blow-fill-seal technology when used for aseptic manufacturing of sterile products. From the relatively limited data available, differences between conventional aseptic processing (1) and from BFS processing, such as duration of fill and duration of media fill, can be observed. This can be explained by the typical way BFS processing is performed, where filling is normally carried out over relatively long periods of time and without the presence of operators in the filling room. This is also reflected in the duration of the media fills, which are significantly longer than those reported for conventional processing in the PQRI survey (1).

Most noteworthy is the large reported difference in media fill contamination rates between BFS and conventional filling when the results of the BFS and PQRI survey (1) are compared.

Contamination Control

It is generally recognized that airborne contamination risk to any aseptic process mostly depends on the level of

contaminants, air movements and their dispersion patterns, and the exposure of the particular product (8).

Regulators have focused on minimizing the challenge by giving good manufacturing practices (GMP) guidance, for example, on the maximum allowed numbers of microbes (colony-forming units) present in the filling environment (4, 5). The most significant source of adventitious contamination in a pharmaceutical filling environment is the presence of operators, who distribute microorganisms either in the form of airborne particles or by transmission by touch. Thus, the higher the operator presence the higher the microbial challenge to the system. BFS technology normally has no operator presence during filling, thereby effectively eliminating the primary source of microbial contamination from the process.

Traditional aseptic processes using pre-formed containers and closures, which require manual handling, rely heavily on the effectiveness of the cleanroom to keep airborne particles (viable and inanimate) at acceptable levels.

The focus of minimizing airborne microbiological concentration addresses the main contamination force, people. One other factor, exposure, is related to the exposed area and the duration of time this area is subjected to the environment. When considering an empty glass vial on a conveyor belt or a stopper resting in a stopper bowl, it is evident that the exposure these components are subjected to is significant compared to a BFS unit, which is formed, filled, and sealed in approximately 10 seconds and indeed is not shuttled at all in the machine while the parison is open.

BFS technology minimizes two important, critical factors of contamination risk parameters, and this is probably the main reason for the consistently robust aseptic behavior of the process as experienced by many operators worldwide. As with all aseptic processes, maintaining control of the process is of utmost importance, and BFS processing is no exception.

Conclusions

The BFS aseptic survey conducted highlights the differences between the use and performance of BFS aseptic filling and conventional aseptic processing using pre-formed containers.

This survey shows that BFS processing is generally used for larger batch sizes and filling of more units over a longer period of time than conventional processes. A comparison of the media fill data from the BFS and PQRI surveys indicates that the failure rate of BFS processes may be lower than one-tenth that of conventional processes.

The robustness of the BFS technique shows that in order to minimize contamination rates during aseptic filling, not only should the contamination sources in the filling environment be minimized but also exposure time should be reduced.

In spite of the clearly advantageous aseptic behavior of the BFS processes, the BFS IOA organization will continue to encourage the exchange of knowledge and investigate possible improvements to the technology to ensure consistent, sterile production.

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