Aseptic advances

Advanced B/F/S allows easy changeover for varied bottle shapes and formats

The latest improvements in aseptic blow/fill/seal technology are streamlining automation of critical processing areas, while limiting human intervention and effectively reducing particulate levels. **Chuck Reed**, Weiler Engineering, describes the implications for enhancing sterility assurance and patient safety

Aseptic blow/fill/seal (B/F/S) systems for the processing of pharmaceutical liquids have experienced rapid and growing acceptance by the pharmaceutical industry over the past 20 years. This has been accelerated by enhancements made to aseptic B/F/S processes based on pharmaceutical industry input and to accommodate the requirements of regulatory agencies.

These enhancements were designed to improve product integrity and help ensure patient safety. As a result, the US FDA and the US Pharmacopoeia now characterise modern B/F/S technology as an 'advanced aseptic process', indicating its use as a preferred technology over other aseptic systems and a better solution for the sterile, aseptic processing of pharmaceutical liquids.

Aseptic B/F/S systems offer a unique combination of flexibility in packaging design, low operating cost and a high degree of sterility assurance. Due to its design and functionality, B/F/S processing inherently produces very low levels of particulate matter, and much of the potential for microbial contamination in its critical areas is mitigated by the absence of human intervention in these areas.

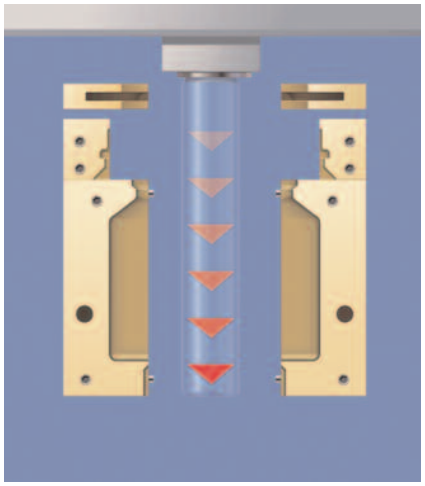
Microbial contamination is a serious issue for companies manufacturing liquid pharmaceutical formulations. Such liquids are ideal growth areas for bacteria such as *Salmonella*, *Escherichia coli* and *Staphylococcus* microbes that have been found in various liquid drug products. A supposedly sterile, but contaminated product may result in deterioration of the drug and loss of potency, and with parenterals can cause pyrogenic reactions after administration to patients.

The majority of liquid drug product contamination in recent decades has occurred in products produced in conventional (non-B/F/S) aseptic processing facilities. In conventional aseptic processing, the drug product, container and closure are subjected to sterilisation processes separately, and then brought together. There is no further processing to sterilise the product after it is in its final container, therefore it is critical that containers are filled and sealed in an extremely high quality environment.

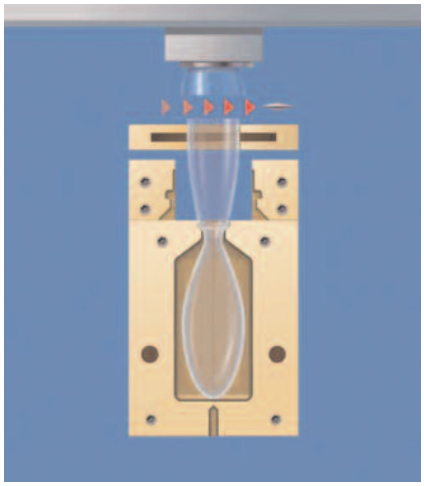
Aseptic B/F/S technology integrates blow moulding, sterile filling and hermetic sealing in one continuous operation to produce aseptically manufactured pharmaceutical liquid products. Unique to aseptic B/F/S systems is their capability for rapid container closure and minimised aseptic interventions.

The most advanced aseptic B/F/S systems are highly automated, designed to require minimum human access and to reduce risk to the product's integrity, while operating in a classified environment. Various in-process control parameters, such as container weight, fill weight, wall thickness and visual defects, provide information that is monitored and facilitates ongoing process control. Its containers are formed from a thermoplastic granulate, filled with a liquid pharmaceutical product and then sealed in a continuous, integrated and totally automated sequence; the critical fill-zone area is shrouded under a continuous flow of positive-pressure sterile filtered air.

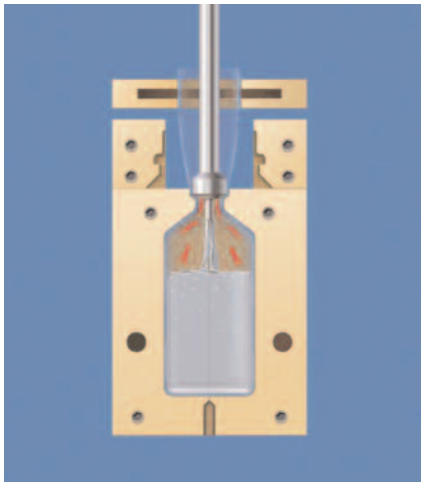
The B/F/S cycle is completed within seconds. This reduces the number of components contacting the product and limits operator intervention, particularly with system changeovers and cleaning. Recent B/F/S equipment designs employ specialised measures to reduce particle levels and minimise potential ▶



Step 1 Extrusion: A sterile homogenous polymer melt (160–250°C) is fed into a parison head which produces a hollow tubular form of the hot resin. The parisons are prevented from collapsing by a stream of sterile filtered support air. Some high-speed machines have up to 16 parisons being formed simultaneously



Step 2 Parison closure: Container moulds close around the parison, and the bottom of the parison is pinched closed while the top is held open in a molten state



Step 3 Blow and fill: The container is formed in the mould by blowing sterile air or creating a vacuum. Filling needles deposit the stipulated volume of product into the container

microbial contamination of the exposed product in the plastic extrusion and cutting zone. Non-viable particles generated during the plastic extrusion, cutting, and sealing processes are thoroughly controlled.

Provisions for carefully controlled airflow protect the product by forcing created particles outward while preventing any inflow from the adjacent environment. This B/F/S zone of protection is continually supplied with HEPA-filtered air by an air shower device (shroud). Air in the critical filling zone meets Class 100 (ISO 5) microbiological standards during operations. Sterile air management within this critical zone is typically verified through environmental monitoring for the presence of non-viable particulates.

Non-viable particles in the B/F/S process primarily originate from the electrically heated cut-off knife contacting the molten parison (an extruded tube of hot plastic resin through which sterile support air passes during the extrusion sequence). Past attempts to manage non-viable particulate generation in this zone of protection were targeted at the removal of particles after they were produced. Included in recent improvements was the development of parison shrouding, which produces a controlled air environment by employing an exhaust blower system with differential pressure controls in conjunction with containment ductwork in the parison cut-off area to siphon away smoke created by the hot knife – a heated high-resistance wire.

A new technology has been introduced to eliminate the generation of the parison-cutting smoke altogether: the KleenKut parison cut-off mechanism.

The device is an automated cold-knife that accomplishes the cutting of the parison without the use of a heated high-resistance wire. It eliminates smoke generation through the application of ultrasonics, effectively reducing particulate generation at the source by more than 99%. The KleenKut mechanism assures that non-viable particles 0.3µm to 10µm in size are significantly reduced in quantity compared with the volume of particles produced during the use of a hot-knife cut-off mechanism.

The FDA's 2004 Guidance for Industry Sterile Drug Products Produced by Aseptic Processing states that the design of equipment used in aseptic processing should limit the number and complexity of aseptic interventions by personnel. Both personnel and material flow should be optimised to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures or the surrounding environment.

It states further that airborne contamination is directly related to the number of people working in a cleanroom and the level of congregation by personnel in areas where critical aseptic manipulations are performed.

Any intervention or stoppage during an aseptic process can increase the risk of contamination. The design of equipment used in aseptic processing should limit the number and complexity of aseptic interventions by personnel.

Challenge studies on aseptic B/F/S systems have been performed over the past 20 years that have correlated the microbial bioburden of environmental air in a B/F/S fill-room to the potential contamination rate of product that is filled on machines in those rooms. These studies have led to an increased understanding of the capabilities of aseptic B/F/S technology in the production of sterile products.

B/F/S system manufacturers should base their product development on such studies, including materials testing specifically for microbial challenges, which have been supported with scientific evidence that the researched machines function within the standards of accredited agencies.

One of the more recent B/F/S challenge studies was conducted in 2004 by Cardinal Health and Air Dispersions entitled 'Evaluation of Blow-Fill-Seal Extrusion through Processing of Polymer Contaminated with Bacterial Spores and Endotoxin'. The study was carried out to further the understanding of the extrusion process and its impact on the quality of B/F/S product. Controlled challenges were conducted to the extrusion system, comprising low-density polyethylene granulate contaminated with *Bacillus atrophaeus* endospores and *E. coli* bacterial endotoxin. The challenge was performed with an advanced aseptic B/F/S system supplied by Weiler Engineering.

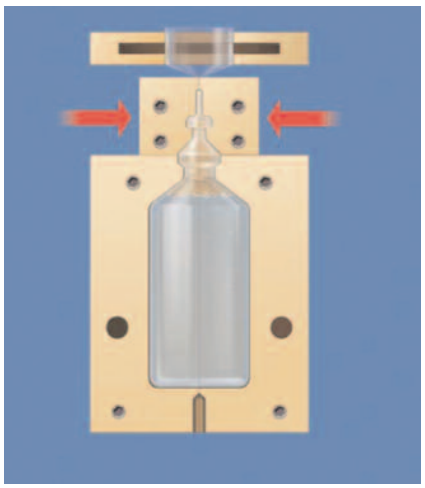
Sterility of B/F/S polymeric containers, materials and processes is validated by verifying that time and temperature conditions of the extrusion, filling and sealing processes are effective against endotoxins and spores. This report states: 'The extruder challenge studies, employing spore polymer and endotoxin polymer, have provided definite evidence for polymer extrusion having the capability to produce vials "free" of viable micro-organisms and possessing acceptable endotoxin levels.'

The challenge study demonstrates a uniform capability of achieving high sterility assurance levels (10^{-6} SAL) throughout the entire process. Even higher sterility assurance levels, approaching 10^{-8} SAL, have been achieved using high levels of airborne microbiological challenge particles.

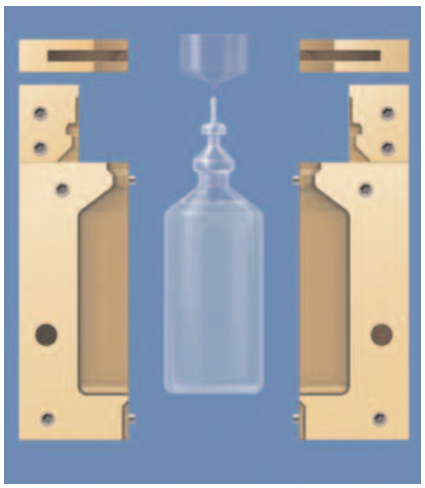
A critical aspect of B/F/S technology is its pyrogen-free moulding of containers and ampoules. Extensive experiments in this challenge study confirm the efficacy of the B/F/S extrusion process, having been performed using high levels of spores and endotoxin-contaminated polymer granules.

Results demonstrated fractional spore contamination levels of less than $1x10^{-6}$, and a three-log reduction in endotoxins with the probability of a non-sterile unit (PNSU) approaching one in one million.

B/F/S processing resins, polyethylene and polypropylene, used to produce aseptic containers for injectables, ophthalmics, biologicals and vaccines are generally considered inert by the FDA, and many of the blow moulding resins used in B/F/S processing have received international acceptance as suitable for pharmaceutical liquids applications. These inert materials do not contain additives, have low water vapour permeability, and are



Step 4 Seal: The filling needles are withdrawn, and the upper part of the mould closes to form and seal the upper part of the container



Step 5 Release: The mould is opened and the completed, filled containers are conveyed to a remote station where excess plastic is removed; the finished product is then taken to final packaging

easy and safe to handle in critical care environments such as hospitals.

Of particular interest within the pharmaceutical industry is the use of plastic material for the B/F/S production of small volume parenterals.

Plastic ampoules offer significant advantages over rubber-stoppered glass vials. There is the safety issue: glass vials are subject to breakage, both in transit and while being administered. Handling glass containers always involves a certain risk of lacerations and glass splinters. Glass ampoules generate a fine array of small glass particles during opening.

Glass is typically transported in cardboard boxes that can contain mould spores, such as *Penicillin sp.* and *Aspergillus sp.*, as well as bacteria such as *Bacillus sp.* Paper, also used in the shipping of glass, can also contain mould spores. The rubber closures used on the glass containers can have mould contamination.

Aseptic B/F/S-produced small-volume parenterals, such as those used for local anesthetics, vitamins, vaccines and other standard injectable products, can be manufactured with a twist-off-opening feature. They can also be combined with a controlled-diameter form in the top to accommodate needle-less spikes. Luer locks or Luer-Slip fits can also be provided for making leak-free connections. For 2–5mL small volume parenterals, syringes can be connected directly to the ampoules without a needle, creating an inherently safer packaging solution.

B/F/S-produced, one piece, plungerless sterile syringes (designed for pre-filling) for use in flushing hospital equipment such as catheters are available for replacing traditional two-piece plunger-type syringes. The B/F/S syringe provides an offset chamber for trapping air, preventing it from being dispensed during drug delivery.

The increased focus on biologics, proteins and other complex solutions has brought B/F/S technology to the forefront. These pharmaceutical products often cannot withstand exposure to high temperatures for extended periods of time without degradation of their active components, making conventional terminal sterilisation an unacceptable method to produce a 'sterile' product.

Temperature-sensitive biological and protein-based products can be processed in advanced B/F/S machines, providing a level of enhanced sterility assurance. Bulk sterilisation, sterilisation by gamma or e-beam irradiation, or filter sterilisation followed by direct packaging utilising the B/F/S process are used successfully for these types of products. B/F/S is demonstrating less than a 1°C temperature rise in a liquid pharmaceutical which is packaged in a 5mL polyethylene vial.

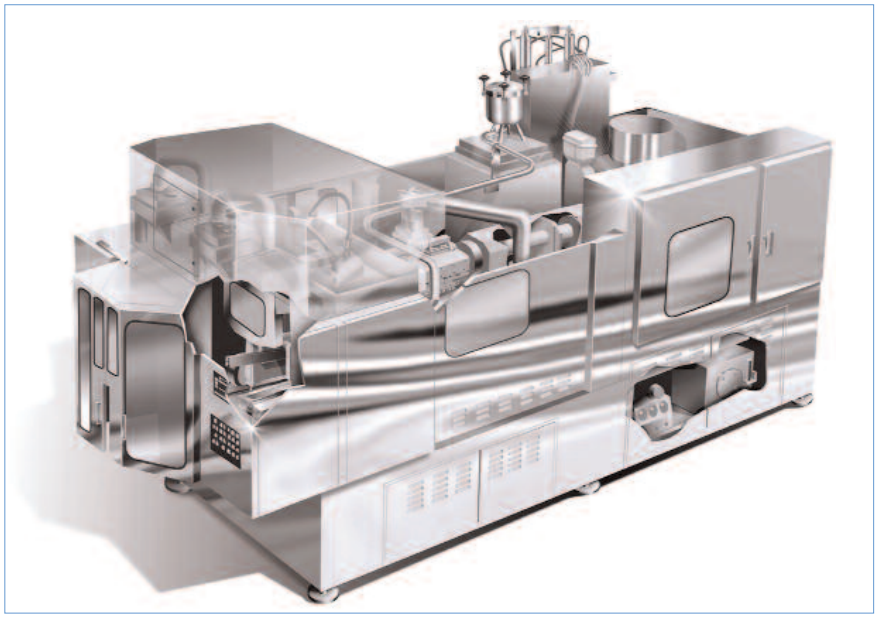
Advanced B/F/S technology can also include the application of insertion technology to permit the incorporation of a sterile tip and cap insert into the blow/fill/seal package to produce a calibrated drop. This process enables increased efficiency and sterility control in the processing of expensive drug formulations for the treatment of glaucoma and other eye diseases.

Other types of sterile inserts can also be incorporated into the basic B/F/S-produced container. Top geometrics for both bottles and ampoules can include a multi-entry rubber stopper or a controlled diameter injection-moulded insert, useful where multiple administration of a drug is required.

Viscous products, with apparent viscosities of less than 15,000 centipoise, and suspension products can be handled by B/F/S machines with specially designed product fill systems. These types of products use innovative liquid-handling systems to maintain multiple-component products in a homogeneous solution during the filling process. Basically, if the solution will flow and if it can tolerate a minimum residence time, it can be packaged in an advanced aseptic B/F/S machine.

The latest advanced models of aseptic B/F/S systems are capable of manufacturing containers ranging in size from 0.2mL to 1,000mL at production rates of up to 15,000 units per hour. Pharmaceutical companies that use such technological advances in aseptic B/F/S equipment design and systems will realise the highest level of quality in the production of their sterile liquid products.

The ability to provide these B/F/S systems, which must meet corporate, scientific, regulatory and end-user requirements, can be quite demanding. These application challenges are being met, however, by continuously evolving and improving B/F/S system and container designs, driven by the need for enhanced product integrity and patient safety. **mc**



Advanced B/F/S machines can produce containers from 0.2mL – 1,000mL

contact

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