A Dedicated Environment

Andrew W Goll at Weiler Engineering, Inc

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Streamlined blow-fill-seal (B/F/S) insertion technology increases flexibility and safety in aseptic packaging of pharmaceutical liquids. Isolators adapted specifically for B/F/S insertion applications – separate, but connected to the B/F/S unit – permit sterile placement of tip-and-cap inserts into plastic metered-dose containers, and rubber/silicone single- and multi-entry stoppers into parenterals, while operating within a dedicated Class 100 environment

The aseptic B/F/S process has proven to be an ideal system for the creation of a wide variety of container shapes and sizes used for packaging sterile pharmaceutical liquids. B/F/S is well suited to producing closed aseptic containers, like injectable products, that need to be opened under critically sterile conditions within a clinical environment such as a hospital, as well as sterile products opened by individuals in work-a-day environments like ophthalmic dropper units. These products must meet the mandates of drug manufacturers and government regulators that require sterile products that will stay sterile until the time of use. Manufacturers also desire the most cost-efficient packaging systems to achieve these ends without any loss of product integrity.

One of the more recent improvements in aseptic B/F/S processing that facilitates these goals is the advance in insertion technology. The latest generation of aseptic B/F/S machines incorporates dedicated isolators adapted specifically for insertion applications. These modular insertion isolators are typically located outside of the classified machine room, separate from but directly connected to the B/F/S unit through a transfer tunnel. The isolator and tunnel are typically sterilised with vaporised hydrogen peroxide and the Class 100 environment within it is maintained by HEPA filtration. This new addition to the aseptic B/F/S system has not only streamlined the insertion process, but has provided a higher level of sterility assurance for products with tip-and-caps and rubber or silicone stoppers inserted under aseptic conditions.

Insertion Applications in Advanced Aseptic B/F/S

Although glass has been the traditional choice for packaging sterile pharmaceutical liquid products, B/F/S-produced plastic containers have emerged as a viable alternative during the past few decades, and particularly with the recognition by the US Food and Drug Administration of B/F/S as an advanced aseptic process, indicating it as a preferred technology over other aseptic systems.

Unlike glass, plastic containers are shatter-proof. Glass vials are subject to breakage, both in transit and while being administered. Handling glass containers always involves a certain amount of risk of lacerations and glass splinters, such as with small volume parenterals, where glass ampoules can generate a fine array of small glass particles during opening.

A critical aspect of B/F/S technology is its pyrogen-free molding of containers and ampoules. B/F/S processing resins, polyethylene and polypropylene, used to

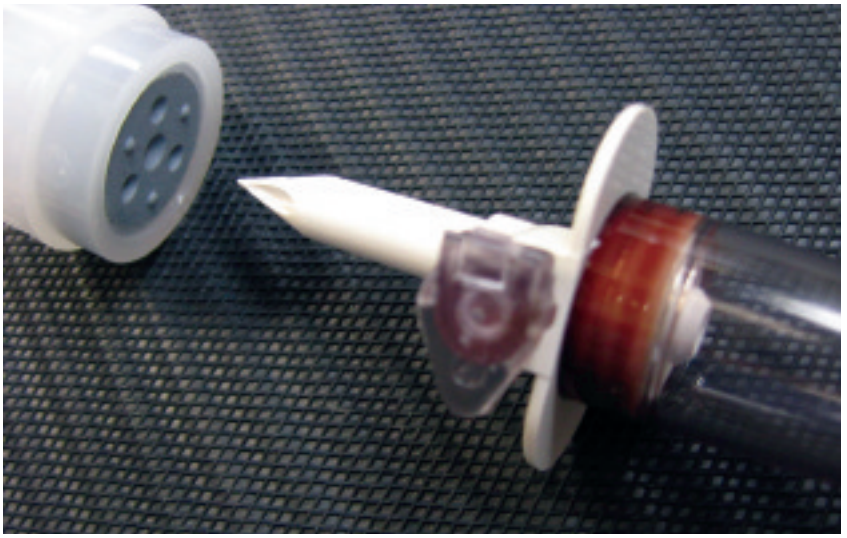
produce aseptic containers for injectables, ophthalmics, biologicals and vaccines are generally considered inert by the FDA, and many of the blow molding resins used in B/F/S processing have received international acceptance as suitable for pharmaceutical liquids applications. These inert materials do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

Other temperature-sensitive biological and protein-based products can be processed in advanced B/F/S machines, providing a level of enhanced sterility assurance. For these reasons the interest in B/F/S-produced plastic containers, and particularly injectable product containers, is continuing to grow within the pharmaceutical industry.

Along with the growing interest in B/F/S plastic containers, the application of aseptically-produced B/F/S containers with inserts has also become increasingly popular. Advanced B/F/S machine designs allow the capability to incorporate the addition of pre-molded, pre-sterilised components (inserts) into the basic container. These inserts, including items such as rubber and silicone stoppers, along with tip-and-cap dropper units for eye drop containers (used to deliver a calibrated drop), are attached to the container after the blowing and filling process prior to the final sealing step. The application of inserts has allowed B/F/S technology to advance and expand into product markets which were previously unavailable, such as intravenous drug administration, solution irrigation and ophthalmic dropper units.

With ophthalmics, the B/F/S insert process enables increased efficiency and sterility control in the processing of expensive drug formations for treatment of glaucoma and other eye diseases. Other types of sterile inserts can be incorporated into the basic B/F/S-produced container as well, such as top geometrics for both bottles and ampoules that can include a multi-entry rubber stopper or a controlled diameter injection-molded insert, useful where multiple administration of a drug is required. The stopper would typically be an FDA-approved, rubber or silicone insert that would be placed inside the bottle or parenteral. Then, at the point of delivery, the nurse would stick a needle through the stopper and extract the fluid, or if it is a vascular flush, the nurse would insert it into the patient's IV set.

Aseptic B/F/S-produced small-volume parenterals (SVP), such as those used for local anaesthetics, 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 to 5 mL 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, and preventing it from being dispensed during drug delivery. Advanced B/F/S insertion processes can also incorporate tamper-evident features for multi-dose container closures, offering added security.

Advanced Insertion Isolation Technology

The latest generation of B/F/S machines use a modular design, integrating duo Class 100-environment manufacturing processes, and utilising servo-drive controls with system-integrated programmable logic controllers (PLCs). These B/F/S systems address process monitoring, streamlined maintenance and consolidated machine components for optimum performance.

They feature advanced insertion technology, incorporating the use of a Class 100 environment isolation chamber located outside of the B/F/S unit, but integrated with the B/F/S machine. This process allows the operator to present a pre-sterilised (typically with a gamma or an e-beam process) component (stopper or dropper insert) through a secure sterile pass-through into a Class 100 environment for insertion within the B/F/S filling shroud.

Sterile inserts are loaded into the isolator through a double-locking, sterile rapid transfer port. The inserts are indexed into a special track mechanism which transfers them from the isolator into the nozzle shroud of the B/F/S. The filling of the container and the placement of the insert into the container both take place in sequential operations within the nozzle shroud. Each component is inserted into a molded container before the final top

closure is formed. The container-insert combination package is then sealed, having given the B/F/S product the intended drug delivery features. The entire operation takes place under Class 100 controlled environment conditions with no human intervention, providing a high level of sterility assurance for the final product.

Key factors of this isolation technology include minimising particles generated through moving components, and controlling the air pressure cascade from the isolator to the nozzle shroud. All of the mechanical features required to get the inserts from the isolator into the B/F/S container are enclosed within a Class 100 environment. A servo-controlled fill and insertion system eliminates the need for hydraulics above the mold. Servo-drives deliver the inserts, so belt and chain mechanisms which typically require lubrication and can generate non-viable particles are eliminated. High-speed PLCs provide integrated control architecture for the entire B/F/S machine. All modular functionality, such as with the insertion isolator, the insert-delivery track system and the B/F/S filling processes are totally integrated for speed and optimum performance. The PLCs receive continuous communication from the B/F/S-isolator system, continually monitoring the differential air pressure in the B/F/S and isolation systems, as well as ensuring that particle counts are under control.

Conventional liquid aseptic manufacturing, with parenterals for example, requires filling and sealing to be carried out in a Class 100 environment and necessitates considerable validation efforts. Both the B/F/S machine and the insertion isolator do not need to be housed in a Class 100 area because their activities are protected within the machines themselves. This protection considerably reduces the scope of validation requirements.

Sterility and particulate matter are two of the most critical requirements for aseptically-produced products, and advanced B/F/S and insertion isolation technology offer distinct advantages over earlier systems. This includes maintaining precise control over differential air pressure between the isolator, the insert transport and the B/F/S nozzle shroud. Both the isolator and the B/F/S system are equipped with HEPA air showers to assure a Class 100 environment under dynamic conditions in the isolator, tunnel and nozzle shroud area.

It has been well documented that in the B/F/S process, non-viable particles primarily originate from the electrically heated cut-off knife contacting the molten parison, and that better control of non-viable particulates will provide enhanced sterility assurance for the B/F/S process. The more advanced B/F/S systems use additional technology in response to FDA concern over particulate contamination during B/F/S fabrication.

Ultrasonic KleenKut® technology can be used to cut the molten parison at ambient temperature, drastically reducing non-viable smoke particles that are generated by traditional hot knife cutting. The process reduces particulates in the cutting area by 99 per cent.

Expanding Use of B/F/S Insertion Technology

Advanced aseptic B/F/S containers and ampoules can deliver precise dosing in disposable formats. The incorporation of a sterile tip-and-cap, a rubber stopper or a multi-entry insert into the B/F/S package offers added flexibility in container design and drug delivery methods, as well as enhanced sterility safety. These benefits are continuing to push the acceptance and use of advanced aseptic B/F/S technology, particularly into injectable product areas and biologics – where proteins and other complex solutions have brought B/F/S technology to the forefront.

The B/F/S process offers outstanding versatility for multiple container designs. A unique design feature of the ASEP-TECH® B/F/S systems, for example, permits the insertion process to be suspended without requiring significant equipment changeover. This feature allows the production of standard containers without inserts to be produced on the same machine with a simple recipe, and tooling change. As the use of advanced aseptic B/F/S processes broaden, insertion technology will become more important as drug producers continue to seek new delivery methods for breakthrough drugs.

About the Author

Andrew W Goll is Technical Sales Manager for Weiler Engineering, Inc, responsible for technical support for the company's customers worldwide. He has over 18 years of experience in the blow-fill-seal community including R&D, design engineering, and contract and generic manufacturing plant operations. He is a member of the Parenteral Drug Association (PDA) and International Society for Pharmaceutical Engineering (ISPE). Andrew holds a Bachelor of Science degree in Business Administration and a Master of Business Administration degree.
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