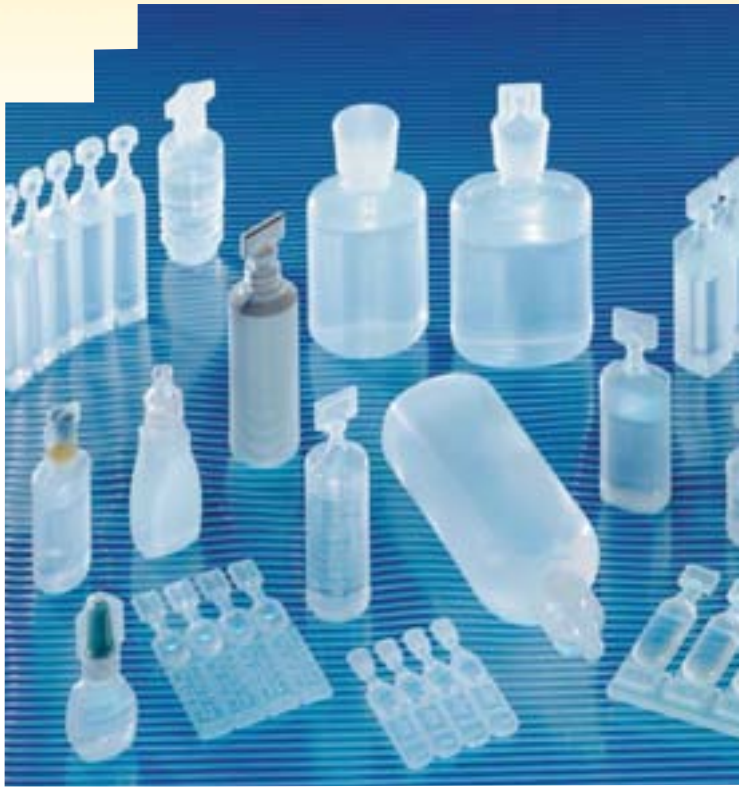
# Advances In Aseptic BFS Processing Of Pharma Liquids Improve Product Integrity And Patient Safety

By Chuck Reed and Wayne Koberstein



Aseptic blow-fill-seal (BFS) systems for the processing of pharmaceutical liquids have experienced rapid and growing acceptance by the pharmaceutical industry during the past 20 years. The latest improvements in aseptic BFS technology are providing more streamlined automation of critical BFS processing areas, while limiting human intervention and effectively reducing airborne microbial bioburden and particulate levels and enhancing sterility assurance and patient safety. Enhancements to improve product integrity and help ensure patient safety — and based on pharmaceutical industry input and regulatory requirements — have accelerated adoption of BFS over conventional systems. As a result, regulatory authorities routinely reference BFS 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.

"BFS has already been established as one of the preferred methods for aseptic processing, along with barrier isolator systems, on the basis of the sterility assurance level that it can provide when operated under controlled conditions," says Patrick Poisson, head of manufacturing at United Therapeutics. "If you examine the design history of the technology, you would find that BFS was at the forefront of minimizing operator presence in critical areas, well before restricted access barrier systems became common on conventional vial lines. Twenty-five years ago, BFS was virtually unknown in the pharmaceutical industry, as its main use was for manufacture of OTC hygiene products. In a relatively short time period, it has become well-accepted worldwide for both inhalation and ophthalmic drug products."

Aseptic BFS technology integrates blow molding, sterile filling, and hermetic sealing in one continuous operation to produce aseptically manufactured pharmaceutical liquid products. Unique to aseptic BFS systems is the capability for rapid container closure and minimized aseptic interventions. Aseptic BFS systems offer a unique combination of flexibility in packaging design, low operating cost, and a high degree of sterility assurance. BFS 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.

For United Therapeutics, BFS was the optimum solution in producing its inhalant for Pulmonary Arterial Hypertension (PAH), says Poisson. "BFS unit dose ampoules are the preferred container/closure system for these types of products, so it was an easy choice for us to make the commitment to install BFS capability in our new facility in Silver Spring, MD."

## UPGRADES IN THE CRITICAL ZONE

Microbial contamination is a serious issue for companies manufacturing liquid pharmaceutical formulations, which present ideal growth areas for bacteria such as salmonella, E. coli, and staphylococcus. A supposedly sterile, but contaminated, product may result in deterioration of the drug and loss of potency and with parenterals can cause pyrogenic reactions in patients. Most liquid drug product contamination arises in conventional (non-BFS) aseptic processing facilities, where the drug product, container, and closure are subjected to sterilization processes separately and then brought together. There is no further processing to sterilize the product once in its final container; therefore, it is critical that

containers be filled and sealed in an extremely high-quality environment.

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, which increase the potential for contaminating exposed product, container closures, or the surrounding environment. It states that airborne contamination is directly related to the number of people working in a cleanroom and congregating in areas where critical aseptic activities are performed.

The most advanced aseptic BFS systems are quite automated, designed to require minimum human access and 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 drug, and then sealed in a continuous, integrated, and totally automated sequence. The BFS cycle is completed within seconds, reducing physical contact with the product and limiting operator intervention, particularly for system changeovers and cleaning.

Recent BFS equipment designs employ the use of specialized measures to reduce particle levels and minimize potential microbial contamination of the exposed product in the plastic extrusion and cutting zone. Nonviable 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. An air-shower device continuously supplies the protected zone with HEPA-filtered air. Air in the critical filling zone meets Class 100 (ISO 5) microbiological standards during operations.

Past attempts to manage nonviable particulate generation in the zone of protection were targeted at the removal of particles after they were produced. Recent improvements included special shrouding that siphons away smoke created by the hot cut-off knife, a heated high-resistance wire. Newer improvements eliminate the hot wire entirely.

## BIOBURDEN UPGRADES

During the past 20 years, challenge studies of aseptic BFS systems have correlated the microbial bioburden of environmental air in a BFS fill room to the potential contamination rate of product filled there. The studies have led to an increased understanding of the capabilities of aseptic BFS technology in the production of sterile products.

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One recent BFS challenge study was conducted in 2004 by Cardinal Health and Air Dispersions, Ltd., to further the understanding of the extrusion process and its effect on the quality of blow-fill-seal product. Sterility of BFS polymeric containers, materials, and processes was validated by verifying that time and temperature conditions of the extrusion, filling, and sealing processes were effective against endotoxins and spores. The report stated, "The extruder challenge studies … have provided definite evidence for polymer extrusion having the capability to produce vials 'free' of viable microorganisms and possessing acceptable endotoxin levels."

BFS processing resins used to produce aseptic containers for injectables, ophthalmics, biological, and vaccines — polyethylene and polypropylene — are generally considered inert by the FDA. Many of the blow molding resins used in BFS processing have received international acceptance as suitable for pharmaceutical liquids applications. The inert materials contain no additives, have low water-vapor permeability, and are 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 BFS production of small volume parenterals. Plastic ampoules offer significant advantages over rubber-stopper glass vials, which are subject to breakage in transit and while being administered. Handling glass containers always involves a certain amount of 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 mold spores and bacteria. Paper used in shipping, as well as the rubber closures on glass containers, can have mold

contamination.

An alternative to glass appealed to United Therapeutics, according to Poisson. "The packaging needs of our inhalation product would be considered fairly typical in that we needed a container/closure system that would be familiar to the pulmonary healthcare community, compatible with our product, and easy for our patients to use," he says. "BFS ampoules satisfied all of the requirements. In regard to ease of use, BFS ampoules offer multiple benefits, especially for treatment of chronic pulmonary diseases, in that the containers are light and easy to transport, do not break like glass, and are easy to dispense into a nebulizer."

Aseptic BFS-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 needleless 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.

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

## INCREASED ATTENTION ON BFS TECHNOLOGY

The increased focus on biologics, proteins, and other complex solutions has brought BFS technology to the forefront. Temperature-sensitive biological and protein-based products can be processed in advanced BFS machines, providing enhanced sterility assurance with bulk sterilization, gamma or e-beam irradiation, or filter sterilization followed by direct packaging. BFS produces less than a one-degree C temperature rise in a liquid pharmaceutical packaged in a 5 mL polyethylene vial.

Advanced BFS technology can also insert a sterile tip and cap into the blow-fill-seal package to produce a calibrated drop, thus increasing efficiency and sterility control in processing expensive drug formations for treating eye diseases. Other types of sterile inserts can be incorporated into the basic BFS-produced container as well, for example bottles and ampoules that include a multi-entry rubber stopper or a controlled-diameter injection-molded insert, useful in multiple drug administration.

Viscous and suspension products can be handled by BFS machines with specially designed product-fill systems. Innovative liquid-handling systems maintain multiple-component products in a homogeneous solution during the filling process. The latest advanced models of aseptic BFS systems are capable of manufacturing containers ranging in size from 0.2 mL to 1,000 mL at production rates of up to 15,000 units per hour, all at the highest possible level of quality in the production of sterile liquid products.

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Producing BFS systems that meet corporate, scientific, regulatory, and end-user requirements can be quite demanding. BFS installation and operation require close interaction with the equipment supplier.

"It is very important to share your intended process with the equipment manufacturer," says Poisson. "Oftentimes their experience allows them to suggest ideas on optimizing performance of the equipment." Facility layout is also a key element, he says. "We spent considerable time on mapping material and personnel flows to make sure sufficient space was allocated for various downstream activities such as inspection, packaging, and waste handling. One challenge that faces any new installation is finding personnel experienced in BFS operations; however, the challenge can be overcome through on-site training performed by the manufacturer's technicians."

Application challenges are being met by continuous evolution and improvement of BFS system and container designs, driven by the need for enhanced product integrity and patient safety. Poisson sees a bright future for the technology. "The full potential of BFS technology is still unrealized. Advances in machine design have improved sterility assurance and now allow for insertion of pre-sterilized components into the container prior to sealing. These capabilities, along with the inherent flexibility of blow molding, provide almost limitless possibilities for future applications. I expect to see the technology expanding into injectables and also playing a role in the manufacture of custom containers designed for interfacing with new types of delivery devices."


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