Advances in Aseptic Blow-Fill-Seal Processing of Pharmaceutical Liquids Improve Product Integrity and Patient Safety

The latest improvements in aseptic blow-fill-seal technology are providing more streamlined automation of critical B/F/S processing areas, while limiting human intervention and effectively reducing airborne microbial bioburden and particulate levels, and enhancing sterility assurance and patient safety.

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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 United States Food and Drug Administration and the United States Pharmacopoeia now characterize 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 like 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 over the past several decades has come about from products produced in conventional (non-B/F/S) aseptic processing facilities. In conventional aseptic processing, 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 after it is in its final container, therefore it is critical that containers be filled and sealed in an extremely high-quality environment.

Automation Upgrades Improve Sterility
Assurance in the B/F/S "Critical Zone"

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

The most advanced aseptic B/F/S 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 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 amount of components contacting the product, and limits operator intervention particularly with system changeovers and cleaning.

Recent B/F/S 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. 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 to 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 was 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 percent. 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 optimized 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.

Reduced Airborne Microbial Bioburden
in Recent Challenge Study of Advanced B/F/S System

Challenge studies on aseptic B/F/S systems have been performed over the past 20 years which have correlated the microbial bioburden of environmental air in a B/F/S fill-room to the potential contamination rate of product which 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, Inc. and Air Dispersions, Ltd. entitled *"Evaluation of Blow-Fill-Seal Extrusion through processing of Polymer Contaminated with Bacterial Spores and Endotoxin"*, a study that was carried out to further the understanding of the extrusion process and its impact upon the quality of blow-fill-seal product. Controlled challenges were conducted to the extrusion system, comprising low-density polyethylene granulate contaminated with Bacillus atrophaeus endospores and Escherichia coli bacterial endotoxin. The challenge was performed with an advanced aseptic B/F/S system supplied by Weiler Engineering, Inc.

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 microorganisms 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 molding 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.

Expanded Options for B/F/S Packaging and Delivery Solutions of Pharmaceutical Liquids

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 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 B/F/S production of small volume parenterals. Plastic ampoules offer significant advantages over rubber-stopper 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 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, such as Penicillin sp. and Aspergillus sp., as well as bacteria like Bacillus sp. Paper, also used in the shipping of glass, can also contain mold spores. The rubber closures used on the glass containers can have mold 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 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.

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 sterilization 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 sterilization, sterilization by gamma or e-beam irradiation, or filter sterilization followed by direct packaging utilizing the B/F/S process are used successfully for these types of products. B/F/S is demonstrating less than a one-degree C temperature rise in a liquid pharmaceutical which is packaged in a 5 mL 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 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. Top geometrics for both bottles and ampoules can include a multi-entry rubber stopper or a controlled diameter injection-molded 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 0.2 mL to 1,000 mL 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 realize 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 a 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.

About Weiler Engineering:

Weiler Engineering is a worldwide provider of aseptic blow-fill-seal custom packaging machinery for pharmaceutical and healthcare applications. Based in Elgin, Illinois, and founded in 1959, Weiler's proprietary blow-fill-seal system is the culmination of 40 years of innovation in machine design and sterile process development, producing a highly advanced aseptic liquid packaging system. Its ASEP-TECH® blow-fill-seal technology integrates blow molding, sterile filling and hermetic sealing in one continuous operation to produce aseptically manufactured products.

The company uses the latest technological advances in equipment design and systems to ensure the highest level of quality in the production of sterile liquid products. Its equipment must meet demanding corporate, scientific, regulatory and end-user

requirements. These application challenges are met through the offering of several machine models designed to manufacture containers ranging in size from 0.1 mL to 1,000 mL at production rates of up to 15,000 units per hour, depending on container configuration.

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