IMPROVING PROCESS QUALITY OF PHARMACEUTICAL LIQUIDS:

ASEPTIC BLOW/FILL/SEAL TECHNOLOGY VERSUS TRADITIONAL ASEPTIC PROCESSING

Here, Chuck Reed, Director of Sales & Marketing at Weiler Engineering, explains how blow/fill/seal technology, acknowledged by the US FDA as an advanced aseptic process for the packaging of sterile pharmaceutical liquids, is gaining increasing acceptance by providing a high assurance of product sterility, eliminating the need for human intervention, improving flexibility in container design and increasing process uptime.

Since its introduction into the North American pharmaceutical market more than 40 years ago, blow/fill/seal (B/F/S) aseptic processing has established itself as a highly efficient and safe system for the filling and packaging of sterile pharmaceutical liquids and other healthcare products, such as creams and ointments. B/F/S product usage has been widely established in the ophthalmic and respiratory therapy markets for some time and lately B/F/S technology has been gaining increasing worldwide acceptance in the parenteral drug marketplace, replacing traditional glass vial processing in a growing number of applications.

B/F/S enables a container to be molded from plastic, aseptically filled and hermetically sealed in one continuous, integrated and automatic operation, without human manipulation. The process provides flexibility in container design and system changeovers, high volume product output, low operational costs and a high assurance of product sterility. The inherent safety of the process – packaging sterile products under aseptic conditions without human intervention – has led the US FDA, and the US Pharmacopoeia, to characterise B/F/S technology as an "advanced aseptic process".

New advances in drug delivery, the desire to improve convenience in handling pharmaceutical products, growing emphasis on combination products, the increasing focus on protein-based drugs and other biologics, and tighter regulatory criteria on product safety, have focused more attention on B/F/S technology as a better solution for the sterile, aseptic processing of pharmaceutical liquids compared with traditional aseptic methods.

PERSONNEL INTERVENTION IN TRADITIONAL ASEPTIC AREAS

Traditional aseptic sterilisation involves handling and manipulation of the material, containers, and sterilisation filling processes with human intervention. It therefore has a higher potential for contamination during processing. The US 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.

A person, walking normally, emits roughly 10,000 skin particles per minute. Such particles can and do hold microbial contamination. A rip in a worker's uniform, a momentary exposed wrist, a mask placed too low on the nose or physical contact with an open fill port will increase microbial contamination within a critical area.

According to the FDA's guide, airborne

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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. Isolation of personnel from these critical areas would eliminate the major source of contamination in traditional aseptic processing.

In traditional aseptic processing, changing or adjusting filling nozzles and heads necessitates the shutdown of the filling operation and requires re-sterilisation of the entire equipment. This increases manual intervention in this critical area. Cleaning and sterilisation which is carried out by personnel, opens the door to breaching of established procedures for microbial decontamination and potential introduction of other particulates like dirt, oil and chemicals.

Mold is common flora found on floors, walls and ceilings of buildings. Contamination occurs due to the retention of water in cracks, edges and joints that are susceptible because of inadequate sealing. Brooms, mops and anything used for cleaning can become contaminated and increase atmospheric contamination because of raised dust or splashing water. In traditional aseptic processing, significant manual intervention is required in critical areas to maintain compliance with established sterile mandates.

ADVANCED BLOW/FILL/SEAL ASEPTIC TECHNOLOGY

In advanced aseptic B/F/S processing, containers are formed from a thermoplastic granulate, filled with a liquid pharmaceutical product and then sealed within a continuous, integrated and automatic operation without human intervention.

Bulk solution prepared under low bioburden or sterile conditions is delivered to the machine through a product delivery system that has been previously sterilised using an automated steam-in-place process.

Modern B/F/S machines (see Figure 1) are fully automated, designed to require minimum human access and operate in a classified environment using the following steps:

(a) granules of a polymer resin, conforming to a predetermined set of specifications, such as polyethylene, polypropylene, co-polymers or other blow-moldable resins, are pneumatically conveyed from a non-classified area into the hopper of the B/F/S machine, from which the plastic is fed into a multi-zone rotating screw extruder which produces a sterile homogenous polymer melt (160–250°C) (see Figure 2a)

(b) then to a parison head which produces hollow tubular forms of the hot resin (called parisons). The parisons are prevented from collapsing by a stream of sterile filtered support air. Some high-speed B/F/S machines have up to 16 parisons being formed simultaneously

(c) container mold(s) close around the parisons, and the bottom of the parison is pinched closed, while the top is held open in a molten state (see Figure 2b)

(d) the container is formed in the mold by blowing sterile air or creating a vacuum (Figure 2c)

(e) filling needles deposit the stipulated volume of product into the container

(f) the filling needles are withdrawn, and the upper part of the mold closes to form and seal the upper part of the B/F/S container (Figure 2d)

(g) the mold is opened and the completed, filled containers are conveyed out of the B/F/S machine to a remote station where excess plastic is removed and the finished product is then conveyed to final packaging (Figure 2e).

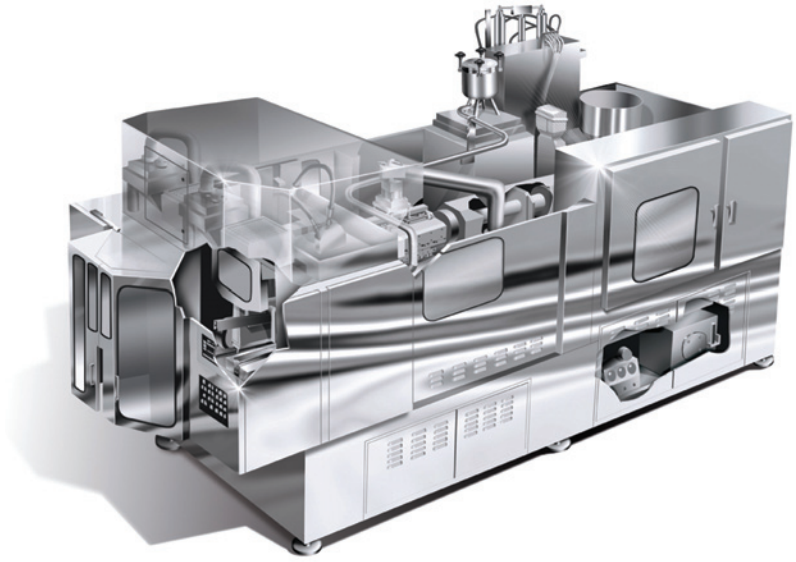

Figure 1: Advanced B/F/S Machines Can Produce Containers from 0.2-1000 ml

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.

The forming, filling and sealing steps are achieved in one unit operation – the cycle being completed within seconds. Automation of B/F/S process steps eliminates manual intervention and reduces risk to the product. No production personnel are present in the filling room during normal operation.

ASEPTIC B/F/S SYSTEM MICROBIAL & PARTICULATE INTEGRITY

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.

Challenge studies have been conducted on the sterility levels of advanced B/F/S technology, which demonstrate a uniform capability of achieving contamination rates not exceeding 0.001% throughout the entire process. Even higher sterility assurance levels approaching 0.000001% have been achieved using high levels of airborne microbiological challenge particles.

Endotoxins are a potential pyrogenic contaminant, essentially dead bacterial cellular

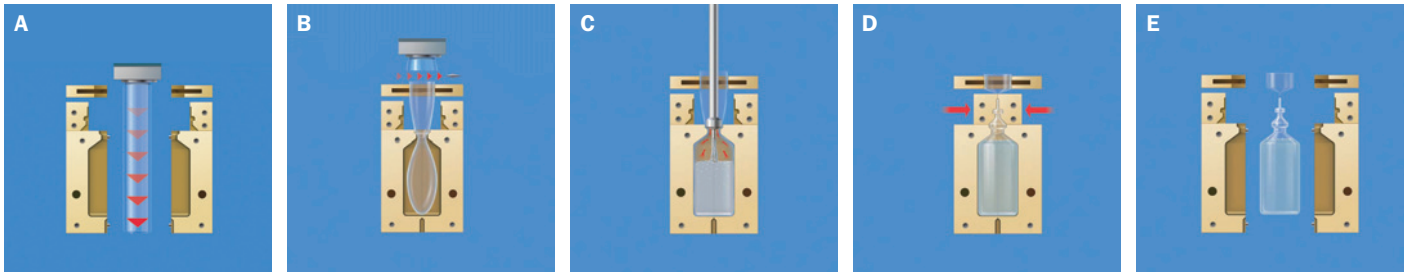

Figure 2: Selected Steps from the Aseptic B/F/S Process: a) Extrusion, b) Parison Closure, c) Container Formation, d) Seal, and e) Release.

matter. They can lead to serious reactions in patients, particularly with those receiving injections, ranging from fever to death. A critical aspect of B/F/S technology is its pyrogen-free molding of containers and ampoules. Extensive experiments confirming the efficacy of the B/F/S extrusion process have been performed using high levels of spores and endotoxin-contaminated polymer granules. The typical B/F/S extruders have demonstrated spore contamination rates of 0.000001%, and 0.00001% for endotoxins.

Control of air quality is critical for sterile drug product manufacture. B/F/S equipment design typically employs the use of specialised measures to reduce microbial contamination and particle levels that can contaminate the exposed product. The B/F/S process inherently produces a very low level of particulate matter and much of potential B/F/S microbial contamination (viable) in the air is mitigated by the absence of manual intervention in its critical areas. Non-viable particles generated during the plastic extrusion, cutting, and sealing processes are controlled. Provisions for carefully controlled airflow protect the product by forcing created particles outward while preventing any inflow from the adjacent environment. These "zones of protection" can also incorporate designs that separate them from the surrounding environment, providing additional product protection.

The B/F/S critical processing zone is continually supplied with HEPA-filtered air by an air shower device (shroud). The B/F/S critical zone is the area where the containers are exposed during filling. Air in the critical zone meets Class 100 (ISO 5) microbiological standards during operations. The critical zone is continuously monitored to ensure a positive differential pressure is maintained between the shroud and the adjacent cleanroom.

PLASTIC CONTAINERS

Domestic US drug companies have been slow to change to plastic, primarily due to the existing installed base of glass production of small-volume parenteral drugs in the US. However, the same is not the case with new drugs that are coming onto the market. These are more frequently being looked at, and submitted for FDA approval, in plastic containers produced by advanced B/F/S aseptic processing. Supporting this move is that the B/F/S processing resins, polyethylene and polypropylene, are generally considered inert by the FDA.

Many of the blow molding resins used in B/F/S processing have received international acceptance as suitable for food and drug applications, and many of the drug products produced outside of the US can be found packaged with these resins.

With the continued refinement of B/F/S technology, its acknowledgment by the FDA as a preferred technology for aseptic processing, and its growing acceptance by drug companies, the migration from glass to plastic containers used for aseptic pharmaceutical liquids is growing rapidly. It has become more cost effective to use plastic containers for aseptic liquids, which effectively costs manufacturers one-third of the cost of glass. Plastic is less expensive to ship because the containers are lighter. For small-volume parenterals, the use of plastic is inevitable, and increasingly being considered for these reasons.

Figure 3: Advanced Aseptic B/F/S Allows Easy Changeover for Varied Bottle Shapes and Formats.

Although many B/F/S systems make available only a limited number of container choices within each container category, some B/F/S machines do allow for broad versatility in container design. Advanced B/F/S machines can design virtually any container mold through the use of sophisticated CAD/CAM technology and 3D modeling. These design systems, when interfaced with the latest in CNC and EDM machinery, ensure fabrication of key components to precise tolerances.

B/F/S machines also allow mounting of separate sterile items (inserts) within the B/F/S container, and in-mold coding and engraving, which provide further opportunities for innovative design over glass products.

FLEXIBILITY WITH CHANGEOVERS GIVES SHORT RUNS, MORE UPTIME, MAXIMUM THROUGHPUT

Modern B/F/S system design is focused on simplicity and flexibility. Many B/F/S machines are configured to produce more than one bottle shape or format. This makes it easy to change over from one container size to another (see Figure 3). One B/F/S machine might produce a family of 2, 3 and 5 ml, then switch to a family of 5, 10 and 15 ml, or to one of 10, 15 and 20 ml, moving from one to the other with relative ease of machine set-up. This is ideal for manufacturers performing contract packaging of aseptic liquid pharmaceutical solutions, because of their need for changeover flexibility.

The growing usage of biologics is demanding packaging in different formats. They usually require smaller process runs and are typically heat sensitive. Many of these new biotechnological drugs do not withstand steam sterilisation or irradiation and so are best treated aseptically. More advanced B/F/S machines have been designed so they can handle these heat sensitive products.

Machine models are available that can produce containers ranging in size from 0.1 ml to 1000 ml at production rates of 15,000 units per hour, depending on container configuration.

B/F/S machine efficiency is very high. More advanced B/F/S machines can approach 99% uptime efficiency, which is significantly higher than traditional aseptic processing which is plagued with slow-downs in part because of manual interventions. To minimise potential system downtime further, some manufacturers are now segmenting their high-volume process lines into more short-run lines, in the event that if one of the lines goes down for maintenance or repair, it will not stop the entire production throughput.

When aseptic throughput is interrupted, or not running because of downtime, the entire process line is affected, which represents a significant production loss to the manufacturer.

AN ASEPTIC TECHNOLOGY DESTINED TO PREVAIL

More rapid container closure processing, elimination of aseptic critical-area personnel interventions, increased system uptime over traditional processing, pyrogen-free molding of containers and ampoules, more flexibility with container design, and an increased capability to capitalise on short runs – these are some of the benefits for manufacturers inherent in advanced B/F/S aseptic technology. And for consumers, increased safety and confidence in their drug products.

These are advances that are significant, if not fully realised yet within the aseptic liquid pharmaceutical marketplace. But it is apparent that advanced B/F/S aseptic technology is destined to become a major player in this arena.