Better drug delivery by design

Advanced plastic packaging makes drugs safer for patients and caregivers.

Pharmaceutical companies are continually developing new drugs and delivery methods, and liquid-drug formulations are no exception. Packaging for these drugs also continue to be updated and refined, and plastics are at the forefront.

The blow-fill-seal (B/F/S) method of packaging liquids in thermoplastics creates aseptic containers that keep contents sterile. Liquid drugs packaged via B/F/S are far less likely to be contaminated with salmonella, *E. coli*, staphylococcus, and other organisms that can cause complications ranging from diminished drug potency to infection.

B/F/S packaging also replaces glass bottles — which can break in transit or while drugs are being dispensed and are often shipped in paper and cardboard that can harbor mold and bacteria.

Blow-fill-seal basics

Aseptic B/F/S combines blow molding, sterile filling, and hermetic sealing in a continuous, automated operation that takes

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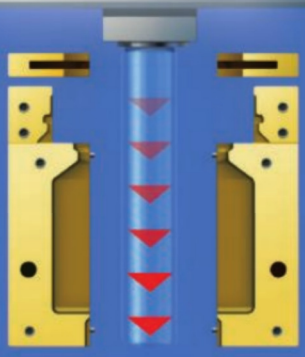
Blow-fill-seal step-by-step



Step 1: Extrusion
A sterile homogenous polymer melt at 160 to 250°C is fed into a parison head, which produces tubes of hot resin called parisons. A stream of sterile, filtered support air keeps the parisons from collapsing. Some high-speed B/F/S machines form up to 16 parisons simultaneously.

place in a clean room. (See "Blow-fill-seal step-by-step.") The cycle takes only seconds with minimal operator intervention. Electronic controls or technicians monitor and record parameters such as container weight, fill weight, wall thickness, and visual defects.

The B/F/S process starts with melted granules of thermoplastics like polyethylene and polypropylene. Sterile, HEPA-filtered air blows the melt into a cavity to create a molten parison, an extruded tube of hot plastic resin. The first stage of a multistage mold closes around the parison, cutting it off at the bottom and holding open the top while air flow continues to push plastic into the edges of the mold.

A heated cut-off knife separates the just-molded container from the extruder. The mold is then moved to a filling station or the air dispenser is replaced with a filling nozzle.

In either case, the nozzle temporarily seals the container's neck and dispenses a preset volume of product. Horizontally flowing sterile, filtered air keeps particles out. Consequently, air in the critical filling zone meets Class 100 (ISO 5) microbiological standards as verified through environmental monitoring. Finally, the package is sealed.

The process works for liquids with viscosities up to 15,000 centipoise, a consistency thicker than honey. Spe-

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Key points:

- Blow-fill-seal processes create plastic vials, fill them with aseptic drugs, and seal them, all with minimal human interaction.
- The extrusion process prevents microbes and endotoxins from contaminating vial contents.
- Containers produced by the blow-fill-seal process can incorporate molded-in features for safer, more-ergonomic drug administration.

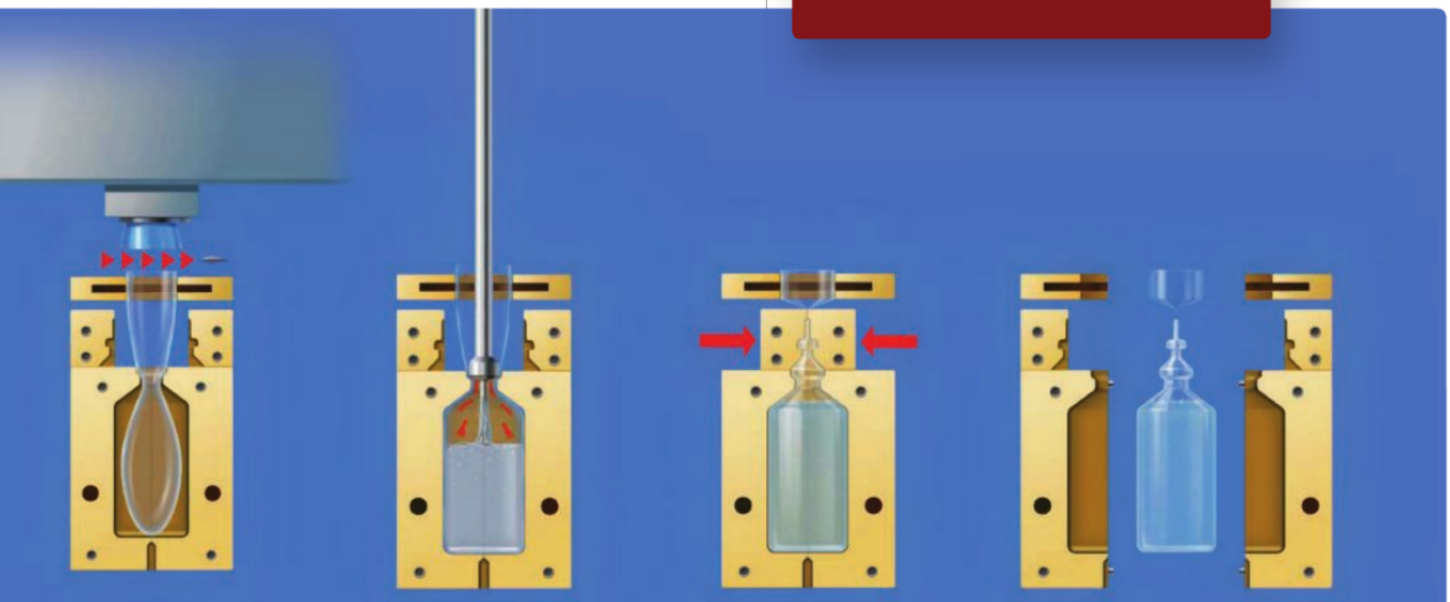
Resources:

Air Dispersions Ltd., *www.airdispersions.com/expertise_expanded.html*

Cardinal Health Inc., *www.cardinal.com*

Weiler Engineering Inc., *www.weilerengineering.com*

"Blow-moldable TPVs Give Silicone Rubbers the Boot," Machine Design, Feb. 9, 2006, *machinedesign.com/article/blow-moldable-tpvs-give-silicone-rubbers-the-boot-0209*



Step 2: Parison closure
Container molds close around the parison. The bottom of the parison is pinched closed while the top is held open and kept molten.

Step 3: Blow and fill
The container is formed in the mold by blowing sterile air or creating a vacuum. Filling nozzles deposit specified volumes of drugs into the container.

Step 4: Seal
Filling needles are withdrawn. The upper part of the mold closes to form and seal the container's top.

Step 5: Release
The mold opens, and a conveyor takes completed, filled containers out of the B/F/S machine. They travel to a station where excess plastic is removed. Another conveyor moves the finished vials to final packaging.

cial attachments accommodate liquid suspensions by keeping components evenly mixed during filling.

The latest aseptic B/F/S systems are capable of manufacturing 0.2 to 1,000-mL containers at up to 15,000 units/hr. Packagers can also incorporate inserts like reclosable tops and sterile tips and caps.

B/F/S liquid packaging has become widely accepted for aseptic operations over the past 20 years. In fact, the U. S. Food and Drug Administration (FDA) and the United States Pharmacopoeia (USP) characterize modern B/F/S technology as an "advanced aseptic process."

Protecting purity

Many advances in B/F/S have focused on keeping bacteria, viruses, and mold spores out of drugs. The FDA's 2004 guidelines for aseptic processing identify operators and others in the clean-room environment as major sources of biological and particulate contamination.

As such, the FDA calls for minimal operator intervention into the B/F/S process. Equipment should be designed for few, if any, interruptions. Any time an operator intervenes, contact should be as brief and straightforward as possible. And there should be as few people as possible in the clean room.

In addition to operator-related contamination, microbes and particulates can get into the packaging via the raw packaging material or from the clean room itself. One area of recent improvement to B/F/S is a mechanism that separates molded plastic from the molten plastic coming from the extruder.

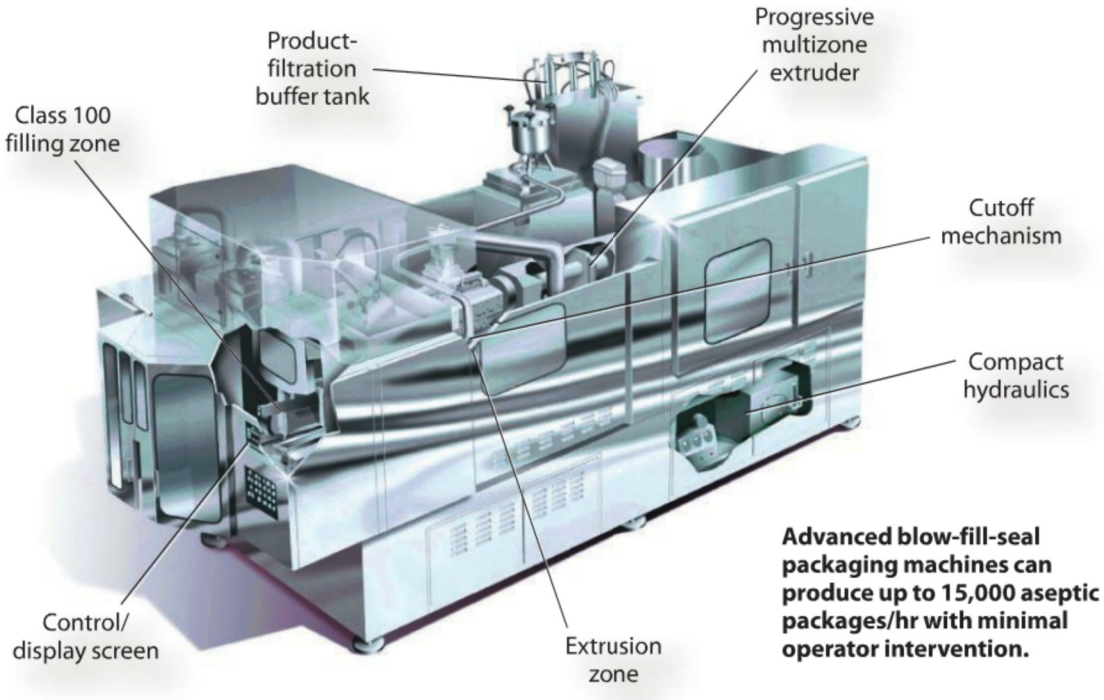
Resistance-heated knives, usually wires, can generate smoke and particulates as they cut through the plastic. They rely on parison shrouding to remove plastic particles from the filling zone. Parison shrouds use exhaust blowers with differential pressure controls and containment ductwork to siphon away smoke.

Newer technologies, like the KleenKut parison cut-off mechanism developed by **Weiler Engineering Inc.,** Elgin, Ill., eliminate the smoke by using ultrasonics instead of resistance heating to cut parisons. Studies show the unheated mechanism produces 99% fewer plastic particles 0.3 to 10 µm in size than hot-knife cutoffs.

Biologic contaminants are of as much, if not more, concern to pharmaceutical packagers as particulates. The FDA generally considers polyethylene and polypropylene resins used in B/F/S packaging to be inert, meaning they don't contain additives, cause reactions in patients, or promote microbe growth. Still, there's the possibility the thermoplastic-pellet starting material could be contaminated with microbes.

For that reason, industry groups have performed so-called challenge studies to assess this what-if scenario. One such study, conducted in 2004 by **Cardinal Health Inc.,** Dublin, Ohio, and **Air Dispersions Ltd.,** Manchester, England, contaminated low-density polyethylene granulate with *Bacillus atrophaeus* endospores and *E. coli* bacterial endotoxin.

It found that the extrusion portion of the B/F/S process made vials that were free of viable microorganisms. And fractional spore-contamination levels were under 1 ppm. Furthermore, endotoxins that bacteria can leave behind — which can cause their own biologic reactions — were



Advanced blow-fill-seal packaging machines can produce up to 15,000 aseptic packages/hr with minimal operator intervention.

Advanced B/F/S machines can produce containers from 0.02 to 1,000 mL in volume. Operators can easily change system molds to vary bottle shapes and formats.

reduced by a factor of 1,000 to within acceptable levels.

Advanced B/F/S processes are considered to have high sterility assurance levels (SALs), a measure used to indicate the efficacy of sterilization techniques. The Cardinal Health study determined that the probability of a nonsterile unit emerging from B/F/S would approach one in 1 million.

Having drug packaging that's sterile from vial formation to drug delivery is vital for modern medicines. Biologics, proteins, and other complex liquids often cannot withstand exposure to high temperatures for extended periods of time without breaking down, preventing the use of conventional postpackaging terminal sterilization. Instead, these drugs can be sterilized in bulk prior to packaging with gamma or e-beam irradiation or filtration, then directly packaged by B/F/S. Studies have shown the temperature of liquid pharmaceuticals rises less than 1°C during B/F/S packaging into 5-mL polyethylene vials.

Vial variables

Recently, the pharmaceutical industry has been particularly interested in packaging drugs in small-volume parenterals. These are single-use or single-patient drug doses administered by injection. In these applications, plastic ampules offer significant advantages over the rubber-stoppered glass vials that were previously used.

First, glass vials can break, both in transit and while being used. People handling glass containers are always at risk of cuts and glass splinters. And glass ampules generate a fine spray of small glass particles when opened.

Second, glass is typically transported in cardboard boxes or with paper to reduce breakage. Both can harbor mold spores such as *Penicillin sp.* and *Aspergillus sp.* They can also act as homes to bacteria like *Bacillus sp.*

Third, mold can contaminate the rubber stoppers used with glass containers.

As noted above, B/F/S for making plastic ampules does not harbor microbes. The flexibility of the molding process means vials for pharmaceuticals used in small volumes like local anesthetics, vitamins, and vaccines can be manufactured with molded-in features; they don't need separate stoppers.

One design uses a twist-off-opening feature. Others add controlled-diameter forms to the top of the vial to accommodate needleless spikes, plastic connectors that let workers transfer drugs to IVs or other containers without syringes.

Industry-standard Luer-style connectors — male threads on the vial that match female threads on needles or standard tapers that form a press fit without threads — can also be molded in for leak-free connections. These allow 2 to 5-mL vials to connect directly to syringe tips without the need to transfer the pharmaceutical using a plunger.

Another design being produced by B/F/S is one-piece, plungerless, sterile syringes. These are prefilled and used to flush hospital equipment like catheters. They replace traditional two-piece, plunger-type syringes and have an offset chamber that traps air and keeps it from entering tubing.

Finally, B/F/S can incorporate sterile inserts into vials. For instance, a comolded tip-and-cap insert can produce calibrated drops of drugs for glaucoma and other eye diseases. Other types of sterile inserts include multientry rubber stoppers and controlled-diameter injection-molded inserts for administering a drug several times. **MD**