4 Reasons Blow/Fill/Seal Technology Should Be Considered For Your Aseptic Filling Needs

Source: Weiler Engineering, Inc.
By Andy Goll

As researchers continue to discover new possibilities in patient care, the need for safe and efficient delivery systems for biopharmaceutical drugs intensifies. For injectable drugs, the most common primary packaging containers have traditionally been glass syringes and vials; however, glass packaging presents several challenges, such as absorption, delamination, glass breakage, risks of breakage, design limitations, a lack of flexibility and multicomponent systems. Multicomponent filling and sterilizing systems present their own challenges when you need to integrate multiple pieces of equipment to accomplish the following in one packaging line: washing, filling, sterilizing, and capping the vials, applying a label, etc. In many cases, special attention needs to be given to incoming raw material control of the rubber stoppers due to the presence of silicone and the potential presence of particulates. This has created pressure on drug manufacturers to come up with alternative methods for a safe and reliable approach to delivering new and innovative life-saving therapies.

One such approach is blow-fill-seal (B/F/S) technology, which is a specialized aseptic liquid packing technology that is considered by the U.S. FDA to be an advanced aseptic process that provides a viable alternative to glass packaging.[1] B/F/S not only addresses the challenges associated with using glass syringes and vials, but the higher automation of B/F/S offers an opportunity to reduce costs, speed up production, and lower labor requirements. Fully understanding the benefits of B/F/S, though, requires a closer look at how the B/F/S filling process works.

How Blow-Fill-Seal Works

B/F/S combines the three steps common with conventional aseptic processing into one completely automated process, under controlled conditions with little to no human intervention.

It includes five basic steps:

1. A thermoplastic resin is melted under high temperatures, and the molten resin is used to form plastic tubes called parisons. During the extrusion process, the parisons are flushed with sterile air. One parison can produce one bottle or up to 10 vials.
2. When the parison reaches the desired length, a mold closes around the parisons. The bottom is pinched closed to form the body of the container, and the top is held open. The mold is then positioned underneath the class 100 filling zone (ISO 5 [Class A]), where the blowing and filling nozzles are stationed.
3. Fill nozzles are lowered into the container until they form a seal with the neck of the mold. If required, the vials or bottles are blown with sterile air to help form the shape of the body of the vial or bottle. Sterile air is vented from the container, as the sterile liquid product is metered into the container with anywhere from 0.2mL to 1000mL of sterile drug product.

4. The seal mold closes to form the top, hermetically sealing the container. (Another form of B/F/S production could allow for the insertion of a rubber stopper insert. This would be placed into the vial after the filling sequence is complete and before the seal molds close.)

5. The mold opens, which allows the formed, filled, and sealed container to be conveyed out of the machine for further processing.

With this highly efficient manufacturing process, a B/F/S container is created under ISO 5 (Class A) aseptic conditions in a matter of seconds. By eliminating the challenges associated with glass packaging, B/F/S offers an improved option for primary packaging applications.

Challenges Of Glass Vials

There are multiple steps involved in the glass filling process that create bottlenecks for manufacturers. The biggest challenge of glass packaging is the presence of particulates coming from either the environment or glass delamination. Particulates can be incredibly dangerous if injected into a patient. This risk requires additional testing during the manufacturing process to ensure that the final product is safe. While inspections are still necessary for plastic, glass inspections must be done much more thoroughly, which leads to the added cost of production. The glass containers must be cleaned, sterilized, aseptically filled, and then autoclaved after they are sealed. There are a number of ways this can be done, either by using a flame process to seal the top of the ampule or by inserting a rubber stopper with a foil-over cap.

Breakage is another major concern with glass, as it can happen at any point during the filling process and even after, during storage and shipping. This presents dangers to employees and even to patients during use. If breakage occurs, careful measures must be taken to ensure it is cleaned up properly, leading to extended downtime. Finally, the lack of flexibility with glass containers limits manufacturers to only a cylindrical design. The ability of the B/F/S process to form any shape of container facilitates global distribution of biologics, which, for example, is critical with vaccines. Glass is also heavier, ultimately adding costs during the shipping process.

Another alternative to glass is form-fill-seal technology (FFS). FFS is completed by bringing two mating surfaces of foil together using a heat seal and then a hot molding process to stamp out and fill the containers. While similar to B/F/S in concept, FFS requires that the internal structure of the containers are, in some way, sterilized prior to filling. You will not have the flexibility in container design or have the opening features and characteristics that make B/F/S unique in so many ways to other conventional filling processes.

Why Should You Consider B/F/S For Your Injectable Drug?

As global regulations demand safer and more efficient ways to deliver drug product, B/F/S and its evolution over the last 50+ years enables better process control, faster filling, and an overall safer drug delivery system. The characteristics of B/F/S and the data supporting its implementation for the delivery of biologic drugs make it a cost-effective method for addressing the challenges of traditional glass filling, which is vital to the future of the global distribution of biologics.[2] Here are four major reasons that manufacturers seeking a filling process for their drug product, especially those targeting the injectable market, should consider B/F/S for their biologic drug:

1. **Sterility assurance** – The high temperatures of the extrusion process for B/F/S sterilize the resin through the residence time in which it resides inside the extruder. This, in turn, sterilizes the inside of the vials or bottles. B/F/S's aseptic process also includes fully integrated clean-in-place and steam-in-place processes that are fully automated and begin with just the push of a button. Automated sterilization-in-place sequences allow for the complete sterilization of the entire product pathway (including product and air filters, if applicable) and any other product contact areas in the system. One of the key aspects to consider when looking into B/F/S technology is that the systems are designed as automated systems, which removes human intervention from the process. The systems also prevent people from coming within close proximity of the filling system located in the Class 100-ISO 5-Grade A filling zone as well as the closed product pathway and its components.

2. **Low per unit cost of production –** For some, the initial cost of capital for a B/F/S machine (which varies per project since B/F/S machines are customizable) can be intimidating; however, the focus should not be on the cost of the machine

but, instead, the per unit cost of production. In a breakdown of numbers, an example is provided where the output of over 4 million vials from a B/F/S machine at .036 cents per vial is compared to the cost when using glass vials with closure only (includes only the cost of the vial, stopper, and cap, and based on pricing provided by a pharmaceutical equipment vendor).[2] The savings per year is estimated at $1.85 million. In a market where millions of dollars are dedicated to manufacturing each year, this could have a major impact on a company's bottom line while increasing quality assurance.

3. **Flexible container design –** Unlike glass, resin can be melted into any shape, opening up new possibilities and, more than likely, cost savings for packaging and shipping of drug products. In addition, changing the shape and size of a bottle/vial on a B/F/S machine can be done in a matter of minutes. Therefore, if a manufacturer has multiple product lines or families of products, they can all be produced on the same machine. What would take around 8 hours on a typical filling machine is reduced to roughly 2 hours with a B/F/S machine. By having flexibility in design criteria that allows operators to change bottles/vials as needed, B/F/S offers yet another way to reduce the cost of capital as well as save time.

4. **Particulates** – Eliminating the use of glass thereby significantly reduces the risk of particulates. Nevertheless, some would argue that using plastic now introduces issues with extractables and leachables (E&L). Yet, in an analysis by Catalent, a leading CDMO in the life sciences industry, data sets in a 24-month compatibility study between glass and a B/F/S vial, ADVASEPT®, were compared for packaging of a large molecule drug product.[3] A monoclonal antibody was formulated and then filled in both vial types. While it is difficult to extrapolate data for large molecules due to the varying responses that can occur, the tests indicated that B/F/S technology was a viable option for primary packaging of biologic drugs.

Overall, advancements in science and technology are creating opportunities to develop new therapies for a wide range of diseases. Yet, without an efficient and reliable method for packaging and delivery, pharmaceutical manufacturers face a bottleneck that could

impact their ability to bring safe and effective drugs to patients around the world. B/F/S offers a solution to this problem while also reducing costs and giving companies the confidence to do business in a dynamic but exciting market.

1. FDA (2004) *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practices*, Retrieved from https://www.fda.gov/media/71026/download
2. Goll, Andy. (2017). *The Cost Savings Of Blow-Fill-Seal: More Than A Million Reasons To Switch*. Pharmaceutical Online. Retrieved from https://www.pharmaceuticalonline.com/doc/the-cost-savings-of-blow-fill-seal-more-than-a-million-reasons-to-switch-0001
3. Hartzel, Bill and Goll, Andy. (2017). *Blow-Fill-Seal For Biologics: Breaking Through The Glass Ceiling Of Pharmaceutical Packaging*, Pharmaceutical Online. Retrieved from https://www.pharmaceuticalonline.com/doc/blow-fill-seal-for-biologics-breaking-through-the-glass-ceiling-of-pharmaceutical-packaging-0001