apijectTM insights

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The Surprising Strengths of Blow-Fill-Seal

Why does the FDA calls BFS an "advanced aseptic process"? How does BFS combine high-speed, economically efficient production with notable manufacturing flexibility? Respected industry veteran Philip Leslie explains "the basics of BFS."

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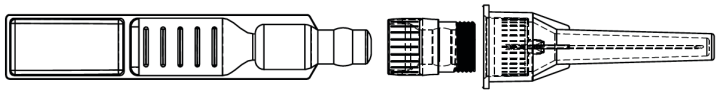
Philip Leslie is a leading global pharmaceutical executive with well over three decades in manufacturing leadership roles for some of the world's leading pharma companies including GSK, MSD and Eli Lilly.

At some point in our lives, almost all of us have used a squeezable plastic bottle to self-administer eyedrops or nasal spray. But it's surprising how little is understood about the technology that manufactures these simple yet remarkable containers, even among the industries that rely on this process.

The manufacturing technology in question is called "Blow-Fill-Seal," or BFS for short.

What follows is an overview of the basics of BFS technology and why our device technology company, ApiJect Systems, Corp., has selected BFS to manufacture a new kind of Prefilled Injector* that can help make injections of vaccine and medicine safe and accessible for everyone in the world.



An innovative combination of two proven elements

We believe our BFS Prefilled Injector is an innovative marriage of form and function, but its basic design is a simple, straightforward combination of two proven components: a BFS container and a pen-needle style hub, much like that used for millions of injections every day around the world.

* The ApiJect Prefilled Injector has been submitted for review but has not yet been cleared by FDA or other regulatory authorities.

The many proven strengths of BFS make it the obvious choice to create the liquid drug or vaccine container for our Injector. To begin with, BFS is well-established and almost universally accepted. Today there are probably thousands of BFS machines in operation around the world, collectively producing up to 50 billion aseptically filled containers per year.

BFS containers also are used for hundreds of non-injectable sterile liquids (such as respiratory products, eardrops, eyedrops, nasal sprays, orally consumed medicines, etc.), plus a wide range of food and beverage products, and even cosmetics and other goods.

Two basic types of BFS machines: shuttle and rotary

BFS enables high-speed, high-volume, aseptic manufacturing, filling and finishing of sterile liquids. This is accomplished through two styles of manufacturing machines: the original "shuttle" style and the "rotary" style, featuring an improved process.

ApiJect uses rotary-style BFS manufacturing machines rather than the older shuttle-type machines. Advantages of rotary machines, which have become available only in the last decade or so, include very high speed; aseptic quality assurance; and less waste byproduct (i.e., there is less excess polymer that must be trimmed from the finished unit).

The speed and productivity of high-end rotary BFS machines can be measured in a couple of ways. The entire process of blowing a container, filling it and sealing it can be done in 3 to 7 seconds by a rotary machine, compared to a 10-15 second process for a shuttle machine. Because of this high speed, a single rotary machine can produce up to 25,000-unit dose containers per hour with high "up time" adding to the productivity.

Most of this greater speed is due not to a faster-moving assembly line per se, but to less wasted motion. In a shuttle type BFS machine, the plastic vials literally shuttle back and forth as they are created, filled and sealed. The containers are formed in one position then need to shuttle back to another position for filling. By contrast, a rotary machine uses a smooth, zipper-like action where a series of molds, each split into two halves, are continually coming together like two interlocking gears in a fluid, graceful process. For anyone who appreciates elegant engineering, it's a beautiful thing to watch.

- Aseptic quality can be enhanced in rotary style machines because the filling needles are located inside an enclosed polymer chamber called the parison, not in the open air. This may reduces the chances of contamination and particles getting into the process.

There are several reasons why BFS is considered an advanced aseptic process:

- BFS uses plastic rather than glass. The polymer is heated up just before the container formation process (the "blowing" phase of BFS). This heating factor has a sterilization effect on the polymer. We know this occurs as generally in the validation of the machine the bioburden of the polymer is increased and shown not to create a contamination in the formed vial/product.

- The second reason why BFS is an advanced aseptic process is that it's a highly automated operation, with minimal human intervention required from the beginning to the end.
- Third, the BFS process of forming, filling and sealing operates in a sealed parison with positive air pressure systems that keep out particles.
- Fourth, the sheer speed of the BFS process means that the vial or container is formed and sealed within a few seconds, which reduces the opportunity for any contaminants to get into the container.

Shuttle style BFS machines have different strengths

Keeping all of this in mind, it remains the case that shuttle machines are a more practical choice for certain applications.

For example, certain large-volume parenterals – up to 2 liters – are easier to fill and handle on a shuttle style machine. Smaller runs are sometimes more practical on a shuttle machine (or a Rommelag Model 434 rotary machine).

Insertion technology is where a septum or pre-molded insert are added to the container before sealing, this is only possible with shuttle machines.

Finally, shuttle machines can be more flexible than rotary machines, in the sense that you can change molds more easily, making it possible to manufacture a range of different products on each machine.

How rotary BFS delivers high productivity and cost-effectiveness

Rommelag®, ApiJect's machine supplier, makes two different rotary BFS models. Model 460 is designed for high-volume production, while Model 434 is has a single mold and produces a smaller output per hour. Although the 434 has a lower output, it is ideally suited to more niche production runs.

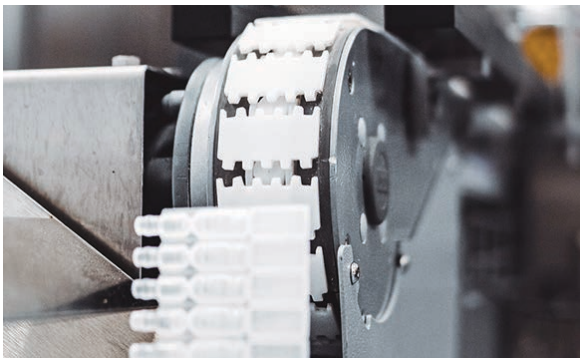
Materials reliability is also an important strength of BFS. Blow-Fill-Seal technology has a simplified supply chain. For example, ApiJect requires only pharmaceutical-grade plastic resin and stainless-steel cannula in order to produce our BFS Prefilled Injector.

BFS does not require shipping, storage, cleaning and re-cleaning over a period of days or weeks for the raw materials that are associated with traditional formats and materials. As noted, the container is produced, filled and sealed in seconds.

The high automation factor means less human labor is required, Two or three people can run a BFS production line, whereas several people are typically required to run a fill-finish line for glass vials.

In addition, with BFS there is no need for stoppers, crimps, washing stations, or depyrogenation (a specific form of sterilization for injectable drugs). This reduces the complexity and the physical footprint of BFS, in turn driving a smaller capital outlay for the high-end air conditioning units needed for a smaller clean room.

Flexibility and economy in mold prototyping and creation



Finally, another important advantage of BFS is the capacity to be very flexible about creating new and different molds, which drive the production of containers in different shapes, sizes and thicknesses. All of this can be precisely calibrated and customized for a specific product that is being contained in the BFS vial.

Creative design of an eyedropper bottle, for example, would allow you to produce a container that if squeezed gently, expels just a couple of drops of liquid, but if squeezed more firmly, delivers a larger or more continuous flow of liquid.

Stability: the ultimate test of BFS

With so many validated strengths of BFS, it might raise the question, why would anyone hesitate to use this format for injectables?

When the world's first BFS vaccine factory was built several years ago, pharmaceutical companies and regulators were understandably focused on the issue of stability. to ensure that high-quality results were obtained not just the first time, and not just in a few dozen preliminary tests, but every time through hundreds and then thousands of batches.

That's a significant challenge, and one that absolutely must be met in order to ensure the utmost in quality and patient safety. All pharmaceutical manufacturing and packaging processes require exacting and knowledgeable operation, with a clear understanding of the precise "dial settings" for every control on every machine on every batch. These details vary according to the drug or vaccine being tested; they cannot be assumed to apply to all substances in all circumstances.

The team accomplished this by performing an extensive risk assessment of the process and from this exercise it was determined the critical parameters that were needed to control. The team also performed experiments to determine the design space within which we could operate. The outcome of these set-ups was a process that was predictable, produced a quality product each time, and offered confidence In the delivery.

Based on process understanding and the strength of the design and manufacturing teams at ApiJect, I am confident that our BFS Prefilled Injector will similarly earn the confidence of the pharmaceutical industry around the world – and will play a constructive role in "making injectable medicines safe and available for everyone."