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JUNE 22, 2022

How Blow-Fill-Seal Delivers Operational Efficiencies and Aseptic Fill-Finish

A pharmaceutical industry expert discusses the technical factors and requirements that make BFS an "advanced aseptic process" for fill-finish, and why BFS has relatively low capital requirements

A CONVERSATION WITH JOE WOJCIK
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Joe Wojcik has devoted over 14 years to the pharmaceutical industry at companies including DDL, Inc., Upsher-Smith Laboratories, Lifecore Biomedical, Catalent Pharma Solutions, and MilliporeSigma. Across these organizations his responsibilities have included technical development, management consulting, vendor management, and product development.

INTERVIEWER: Joe, why has Blow-Fill-Seal (BFS) emerged as a viable alternative system for the fill-finish of sterile injectables?

JOE WOJCIK: Until this point, BFS has mostly been used to manufacture simple containers for sterile pharmaceuticals, mainly ophthalmics and nebulizer medicines. By combining a unit-dose BFS container format with the needle integrated into the device, you can get the benefits of BFS, from a flexibility, scaling, and higher-quality standpoint with the basic functionality of a prefilled syringe. You also get the advantages of BFS fill-finish, which includes accelerated production at scale, and—in the FDA's language—an "advanced" aseptic processing system.[1]

To implement this new injection system, what physical attributes and requirements would apply to the facility?

Implementation is easier than one might think. This is due to the modular design of BFS operations. The BFS machine itself is self-contained. Drop it in a room, connect the utilities and put up the clean room walls. The ancillary inspection and packaging equipment can be rolled into place or BFS units can exit the machine for offline inspection and packaging.

Also, the specific location within the facility has implications when it comes to material flow. In this case, most facilities have fixed assets already in place such the location of the dock, the locker rooms, and the test lab that cannot be easily or economically relocated. However, since a BFS production line is a modular design, facility planners can drop the fill-finish operation in place where it makes sense, and build the modular infrastructure around it.

Sterility and particulate matter are two of the most critical requirements for aseptically produced products. How does BFS perform in these areas?

First let's discuss sterility. Because the BFS container is formed, filled, and hermetically sealed in a much smaller "critical zone" than is typical with other filling technologies, BFS can be thought to have definite advantages. According to the FDA, "Advantages of BFS processing are known to include rapid container closure processing and minimized aseptic interventions."[2]

These advantages derive in part from the fact that the critical zone in a typical Rommelag® 460 BFS setup is about the size of a suitcase, where in a traditional filling technology setup, it's the size of a hallway in a home. This is because with traditional modes, the containers must physically travel on conveyors to each station in the process (washing, sterilizing, depyrogenation, filling, and finally sealing).

As for particulates, when you think about particulate matter in a filled and finished drug product, you could say it's either "intrinsic" or "extrinsic." Intrinsic meaning the particles originate from the drug itself (precipitation, aggregation, crystallization, etc.). Extrinsic meaning the particles are introduced somewhere along the way (hair, dust, particles sheading from the container).

In the context of this discussion, if we assume we are filling the same drugs in either traditional modes or in BFS, we can table the "intrinsic" source of particles and focus on the extrinsic. From a formulation and filtration standpoint, traditional modes and BFS utilize the same basic process so we can reasonably say they are on a level playing field until you get to the filling needles. In BFS, the container is formed in a matter of seconds before the needles fill it. Note that critical zone is the size of a suitcase.

Recall our previous discussion about the traditional line and the amount of physical distance the open containers need to travel in the critical zone. The open container is traveling along a conveyor with an open top until it comes to the filling station, and then it's still open until it gets to the capping station. Yes, in a traditional filling line there are controls in place to ensure sterile and essentially particle-free air is showered over the open containers as they travel along the process.

On the extrinsic front, we've covered particulates being introduced into the container. Now let's discuss the containers themselves. The common polymer used in BFS is LDPE (or low-density polyethylene). This material, when formed into a drug container, is relatively soft and flexible, traditional containers, for example glass, is harder and more brittle. But, now take the filled and finished containers, handle them for inspection and packaging, load them on a truck and shake, rattle, and roll them to the last mile until they get to the point of use. This can cause traditional containers to break or shed particles into the drug product. BFS containers, being made of plastic, are highly resistant to breakage, and not generally known for shedding particles.

What is the difference between advanced aseptic Blow-Fill-Seal Technology vs. traditional aseptic processing technology? What is the human operators' relative impact on presence or absence of particulates?

The key differences between the two technologies are 1) primary container materials of construction (polymer with BFS and glass with traditional aseptic) and 2) the complexity involved to get from container to finished good. In BFS, the container is formed, filled and hermetically sealed in a matter of seconds. The output is a sterile pharmaceutical product.

In traditional aseptic (assuming glass vials), the containers are made in one factory, packaged, shipped to a fill-finish facility, unpackaged, cleaned, sterilized, depyrogenated, filled, capped, and then over-capped. Prefilled syringe filling is an equally complex process.

As for human interaction: For BFS the containers are formed, filled, and sealed inside a closed compartment, which prevents human interaction with product contact parts during this process. With traditional aseptic processing, the avenues for human interaction have been greatly reduced, but some gaps remain. Namely, RABS (restricted area barrier systems, aka "isolators") have greatly reduced the human interaction-based source for particulates. However, human interaction can still happen through glove ports and through aseptic interventions. It's during these events where handling issues can cause glass breakage and human sluffing into containers.

How does BFS positively impact operational efficiencies?

Operational efficiencies can be thought of in three general categories: People, Process, and Technology. In the context of BFS manufacturing for pharmaceutical products, BFS is inherently designed to be efficient. When up and running, intervention from people is not part of the BFS operating principle. Yes, people need to monitor the machine parameters and sample product for in-process checks. But the machine itself is self-sustaining with automation feeding the resin and conveying filled and finished product to the inspection and packaging processes.

This folds into the process which BFS is designed upon. This process relies on a heavy dose of automation with a phenomenal run rate. Batch sizes and the subsequent changeovers for downtime become risk mitigation strategies based on the value of the drug, product-market considerations, and a various number of other factors.

Although there are many attributes about BFS technology that make it efficient, let's focus on containers. Inherent to the design, the filled and finished container is formed at the point of filling from resin pellets. Looking at modes of filling product in a primary container for other similar pharmaceutical applications, an observer will quickly realize that most every other technology relies on that primary container being manufactured at another location, from which it's shipped to the filling and finishing site for unpacking and handling. While operational factors

can vary from one facility or one drug to another, the BFS machine and its fill-finish process on the whole are designed to be efficient.

How are filling efficiencies determined?

Besides the common metrics measured in the pharmaceutical space, efficiencies in filling are heavily weighted on two related factors, change-overs and batch sizes. Changeovers mean product is not being produced and you get fewer changeovers with larger batch sizes. Luckily, because BFS is design to constantly run, the batch size can be as large as a company requires.

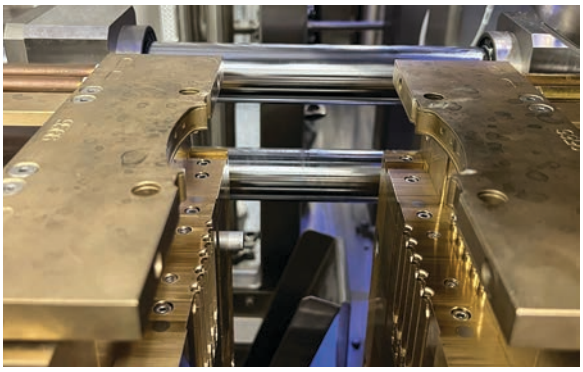
What is the size and technical configuration of the internal chamber in a BFS 460 model where the plastic container is formed, filled and sealed?

First I want you to go back to your grade school days and imagine a cross-section view of the earth. That's kind of how you can think of the critical areas of a BFS system. In the center core is the most critical zone where drug product is not in a closed system and the containers are not yet closed systems themselves. This is the area or "layer" where an ISO-5 environment is maintained.

Now move out one layer to the rest of the inside of the machine and the surrounding suite where the BFS machine resides. This area is commonly maintained as an ISO-7 environment. Move out one more layer to the packaging area and other surrounding area around the suite. This area is commonly maintained as ISO-8 or uncontrolled, depending on the facility and other activities happening in the room.

What determines whether an environment is rated ISO-5?

ISO room classifications have to do with the number of microscopic particulates allowed in a given amount of space, and also the number of air exchanges required per a given period of time. When you think about the ISO classifications as it pertains to the BFS system, it's also important to think about the pressure differentials between classification areas. For example, when comparing the ISO-5 area to the ISO-7 area, the pressure inside the ISO-5 area is relatively higher than the ISO-7 area. Same idea when comparing the ISO-7 area to the ISO-8 area. This is to ensure a positive flow of 'cleaner' air to the "dirtier" air.



How much setup time and downtime for maintenance is required for a BFS production run?

Setup between batches is also known as "changeover." The biggest contributing factor in the changeover of a BFS line is the molds. Are you changing the molds or leaving them in? Thinking about the ApiJect™ delivery system, a mold changeover may not be required between batches as a single ApiJect™ delivery mold setup is appropriate for many injection products. At a minimum, a volume insert may get changed out between runs, which is on the magnitude of a few hours. If an entire mold needs to get swapped, that will take a shift or two, depending on the complexity of the outgoing and incoming mold designs. Also to be considered is that the parison head has different geometry for different resin types. This change alone is on the magnitude of a shift or two.

Assuming the molds and/or parison are not touched during changeover, the benefit of the BFS system is the integrated and automated CIP cycles to flush, clean, and prepare the system for compound of the next batch. In a highly tuned organization, the preparation and formulation of the next campaign is starting as the filling tank of the "current" batch is coming to an end. Once the current batch ends, the next one can start to be filled in a matter of a few hours.

BFS systems are robust and do not require frequent invasive maintenance. It's common for an organization to have an annual or biannual facility shutdown where BFS machines are taken offline for mechanical and preventive maintenance. If a good maintenance system is in place, BFS machines can run non-stop in-between schedule maintenance periods.

BFS proponents say this technology offers a unique combination of speed and scale. Can you put some dimensions to those claims?

BFS machines are designed to run continuously. Nevertheless, batch changeovers happen, facilities shut down for periodic maintenance, and operator scheduling needs to be considered. Even when accounting for downtime the fill-finish process can result in some very impressive output numbers for Blow Fill Seal.

Let's run the numbers. Take a Rommelag® 460 machine with a 25 unit-dose mold configuration that runs at a standard 3-second machine cycle. The simple math on that machine running 24x7x365 is roughly 260 million units per year. But that's not practical for the reasons we stated above. Assuming the machine runs 300 days a year at 80% up-time, we get just over 172 million units per year for one BFS machine.

Does BFS significantly lower capital requirements?

Comparing BFS against other glass filling technologies (not considering downstream inspection and packaging, as they are roughly the same between BFS and glass technology), BFS offers a clear advantage from a capital outlay standpoint. I'll give a few examples.

First, machine footprint: BFS has a much smaller physical footprint compared to the equivalent throughput traditional glass technology, this results in small building requirements for BFS when looking to match the same glass throughput.

Second, HVAC: Because the critical zone in a BFS machine is much smaller than comparable traditional filling technology, this means less HEPA filters, less HVAC equipment, and fewer air exchanges, which can contribute to overall lower capital requirements to set up, as well as a lower operational cost.

Third, raw material storage: With traditional glass, the components are received into the facility, where they need to be handled and stored prior to feeding into the equipment for further preparation before filling. With BFS, the only input to make a container is pharmaceutical-grade LDPE resin pellets, which can be stored in a silo. With filling using traditional technology, the facility's infrastructure needs to be designed and built to handle the complexity of storing and

handling components. With BFS, an exterior silo is built and the pellets are automatically vacuum transferred directly into the BFS machine when needed.

Does BFS support a modular manufacturing approach?

"Modular manufacturing" for pharmaceutical manufacturing of injectables can fit into two general categories. And BFS happens to fit into both of them. In the first case, modular would refer to the ability to establish and add-on to the existing state in an easy fashion, like building with Legos®. In the second case, modular would refer to the ability to (1) move different pieces of equipment around, in an easy/defined fashion; and (2) utilize the different pieces of equipment for different tasks.

When it comes to modularity in terms of establishment and adding-on to existing: The BFS machine is a self-contained unit that takes pharmaceutical grade resin, liquid drug product, and a few utility inputs to create sterile pharmaceutical products. Consider it as the anchor in the setup.

Thank you, Joe.

References:

1 From "FDA Compliance Program Guidance Manual, Chapter 56 – Drug Quality Guidance. Sterile Drug Process Inspections," Sept. 11, 2015, p. 8. https://www.fda.gov/media/75174/download

2 From "Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), Office of Regulatory Affairs (ORA), Sept. 2004, p. 50; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice.