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Advances in Sterile Liquids Packaging and Form Factors

Packaging Automation Engineer Jon Burgess discusses packaging factors that have led to wider acceptance of Blow-Fill-Seal technology in the pharmaceutical industry

A CONVERSATION WITH JON BURGESS
General Manager R&D, ApiJect

Jon Burgess has been active in pharmaceutical packaging for 16 years, holding increasingly responsible positions with a pharmaceutical company for over 16 years.

As a Senior R&D Process Manager at an employer before ApiJect, Jon led a team of R&D Engineers responsible for process development, manufacturing support, and equipment acquisition/implementation.

He also managed manufacturing projects as well as pharmaceutical development of drugs for production at the facility.

He oversaw process development of several inhalation, ophthalmic, and injection drugs filled on Rommelag® 460 and Weiler® 640 Blow Fill Seal machines. He further managed the acquisition, design, and implementation of two Schubert packaging lines to expand business into the injectables market.

INTERVIEWER: Jon, thank you for agreeing to speak with us about key advances in packaging and form factors for sterile liquids. To give us a context for understanding recent changes and evolution, can you outline what have been the industry standards in this field during most of the last century?

JON BURGESS: For hundreds of years, the industry has largely relied on glass for packaging sterile liquids. It's an excellent non-porous material with fantastic light and oxygen barrier properties. This barrier protects the efficacy of liquid drugs.

At the same time, glass is fairly expensive. The manufacturing process is relatively slow and cumbersome, involving many steps and machines. Once a glass vial is formed and filled, there is the possibility of breakage and potential flaking.

Given these considerations, one important factor for sterile liquid packaging that has evolved over time is the choice of available materials.

Distribution of products is now more global than ever. How has this impacted pharmaceutical packaging?

Global distribution means requirements for a variety of labeling variations, packaging sizes/counts, and configurations. Packaging equipment suppliers understand that their customers will want to make labeling changes, size changes, and other package variations often and quickly. Therefore, packaging equipment is designed with "format" change parts in mind.

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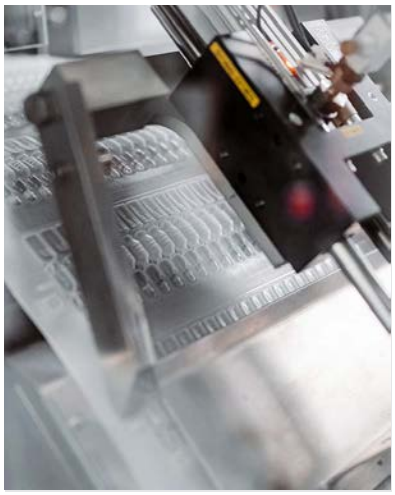


Change parts allow a machine to be flexible in the size or shape of product it can process. Additionally, online printers and labelers can handle many “recipes” which may include different languages, more or less description, or other key elements needed to satisfy the requirements in a given market. Inserters, printers, or other ancillary equipment on packaging equipment may also be enabled or disabled based on the requirements for the product being manufactured.

What are the 5 functions of packaging? How does BFS improve or contribute to improving packaging?

Well-designed packaging does the following for a product.

1. **Protection:** The packaging should maintain the product efficacy and safety over its entire shelf life. Considerations for physical protection during distribution should also be considered. BFS containers are flexible and therefore a good candidate for standard shipping methods.
2. **Containment:** Packaging components should be sized and shaped accordingly to contain the product in its various levels from the unit of use up to the shippable unit. BFS containers are typically contained in foil, cartons, and shipper cases. These are easy to identify, count, and manipulate by shipping entities.
3. **Information:** Printing on packaging materials is essential to satisfying pharmaceutical requirements for drug identification. Product name, strength, NDC code, Lot, and Expiry — along with a myriad of other information — are all provided on the various levels of packaging. Some of this information can be stamped or engraved directly on BFS containers.
4. **Utility of Use:** BFS containers can be sold in packs of several units or as single units, depending on the use case. Containers are designed to be convenient to use and disposable to prevent contamination or re-use.
5. **Promotion:** With modern printing and identification equipment, a BFS package can be filled with useful information, instructions, and warnings for the safe and effective use of the product. The use of logos, symbols, diagrams, and other eye-catching graphics can also be effectively used to make a product stand out among the competition.

What is the difference between conventional terminal sterilization and bulk sterilization? How does this choice impact exposure when utilizing the BFS process?

Terminal sterilization involves sterilizing containers that are already filled and sealed. This is a robust method since the contents of the container cannot be accessed after sterilization, so there is a lessened chance of contamination. Even with the use of terminal sterilization, aseptic or low microbial load methods are used in the BFS process to minimize the initial bioburden.

Bulk sterilization involves sterilization of a product prior to filling, while still in its initial holding tank or vessel. The potential risk in this case is that the product must make its way into the sterile container through the product pathway without being compromised. However, this potential challenge can certainly be overcome with the use of a properly designed and validated sterilization procedure for the product pathway. Bulk sterilization is sometimes necessary in multi-phased formulations.

What does it mean to take a "quality first" approach to packaging?

Good packaging design starts with building quality into the equipment and processes. This means understanding the goals of the process including, the volume expectations, critical parameters, potential defects, etc. The process should be designed to maximize product quality and minimize inefficient steps. Automation can be used to inspect the product throughout the process, ideally removing defects as soon as possible to prevent compounding issues. The process should be monitored for weaknesses with a continuous improvement program in place to give everyone who witnesses the process a tool to make it better.

What new materials are coming to the fore?

Plastics have been around for decades, obviously, but they have steadily come into greater use in pharma, driven by excellent performance.

How have plastic materials evolved to make it a more attractive option for sterile liquid packaging?

Both the chemical composition and the range of available form factors for plastic have improved to address all the ways that drug products need to be stored to maintain stability and efficacy. We have seen huge advances in the ability to combine multiple materials to make packaging components.

In addition, the flexibility of plastic allows you to do so many things with shapes, sizes and visual style or presentation that impact how the drug is provided to the end user. As a result, the pharma world has increasingly transitioned to using a lot more plastics and into flexible materials.

When you started in the pharma industry, what medicines did your company package, and with what kinds of form factors?

My first job in the pharmaceuticals industry was working in a BFS (Blow-Fill-Seal) manufacturing plant. We packaged a lot of drugs for COPD and asthma, such as albuterol sulfate and others. These drugs are filled in a nebulizer, which atomizes the liquid into a breathable form. After a 10 or 15-minute treatment, the airways open in the patient's bronchial system, which allows them to breathe more easily.

We typically had products that were between 0.5 mL and three mL, which is standard for a breathing treatment. The 0.5 mL are usually mixed with a sodium chloride vial to bring it up to three mL or so. We sold them as a brick pack, which is 30 units in a foil pouch, that is basically a month supply for a patient who is getting the drug at home. We also sold a "singles" format that was more popular for the hospitals and clinics. And that is just a single BFS dose, wrapped individually. Those sold very well because they're easily identifiable. They're small, you open it, you use the entire contents, and you throw it away. There's no confusion about using only part of the contents and did I use too much or not enough.

You said one of the advantages of glass is its strong barrier properties. BFS is made from plastic resin, derived from a petroleum base. What are its barrier properties?

BFS typically forms its containers from LDPE, which is Low-Density Polyethylene. This material is permeable to oxygen, light, and water vapor, so we use secondary packaging to protect the product against that possibility. That's where foil pouches come in. The pouches perform the function of the barrier, to protect the drug product from light, oxygen, water vapor loss, or other issues. The pouch is also useful for labeling, product identification data, and so on.

What are the foil pouches made of? Are there any supply chain issues with those constituent materials?

The foil pouches typically are comprised of a couple of plastics, usually including polyester or LDPE. The major material in a foil pouch that creates the functional barrier is aluminum. This is a fairly common metal, with some sourced in China and some sourced in the U.S. Of course, prices of metals go up and down all the time in the global market. Users of foil pouches typically choose vendors partially based on the supply chain strategy of the supplier.

Another advantage you mentioned for plastics is the potential to create a lot of different or customized shapes and sizes for the containers. What range of forms are typically seen in the market and how has that changed or evolved?

I would say most pharma containers are made using BFS have a small nozzle to eject the liquid contents, and they are designed to be either squeezable or flexible enough that when you attach a connector, the liquid can be withdrawn easily.

When it comes to manufacturing BFS containers in different sizes and volumes, there is a wide variety. On the mid-sized range, you've got a number of containers from one mL to 10 or 20 mL that are for irrigation products. A lot of saline goes into 10- or 20-mL bottles.

BFS also enables pharma companies to design custom containers with a potentially infinite range of shapes colors, and thicknesses, because you can easily design and create a new mold that essentially makes any shape of container. This flexible property is not only useful for the functionality of a particular medicine or vaccine, but also for marketing purposes.

How does BFS container flexibility play a role in marketing?

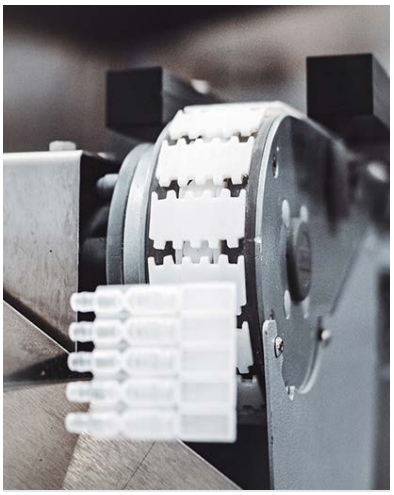
With BFS products, the healthcare worker or the patient can potentially easily identify which drug or vaccine is in the container, often by glancing at the specific shape and color of the bottle. A square blue BFS bottle might be known to the industry be Product X, while a round green BFS bottle might be known to be Product Y. For example, sodium chloride or saline is commonly provided in a pink bottle. So whenever you picked up a pink BFS bottle, chances were very good that it was the saline solution.

Colors are not just marketing tools, but also have an important informational role at times. Color coding of syringes, for example, is standardized with ASTM D4774 which defines colors as they relate to certain products or classes of products so that hospitals can easily identify the contents by the colors of the containers.

This is a valuable factor because hospital personnel work in a stressful environment. They want to be able to look at something quickly and say, “Based on the color, I instantly know at a glance that this is fentanyl 0.5 milligram, or I know this is neostigmine or whatever the drug may be.” We used to joke that, “You know, you should read the label as well.”

As you’re aware, quite a few LMICs (Low- and Medium-Income Countries) have limited refrigeration capacity for cold chain products. Does BFS offer packaging options that address this limitation?

Yes. Relative size and its meaning for cold chain capacity are factors that Western countries take for granted, but the combination of the two is a serious issue for many LMICs. I worked briefly with another vendor who made it clear that all the customer cared about was, “How many cubic centimeters of refrigerator shelf space does your product take up, and how many doses is that?”



BFS can provide meaningful advantages here. In an apples-to-apples comparison of prefilled syringes, for example, one reason that BFS containers can be an attractive form factor is the ability to store a relatively large number doses in a small area, especially if the Needle Hub is shipped separately and does not have to be refrigerated.

Why does BFS require less input and presence from human operators than traditional technologies?

Human presence in the manufacturing space is required mainly during startup of the BFS machine. This is a major event, because you're starting the molten plastic extrusion process; you're making sure your tank of drug product is filled and connected properly to your machine; you’re entering the basic parameters and instructions into the central control unit; you’re checking small maintenance items; and at the same time, you’re filling out required documentation forms. This requires a couple of human operators.

Your Quality Assurance colleagues will be there also, assisting at that time to make sure you get the fill volumes correct, this typically requires a couple of adjustments at the beginning of a production run.

Performing all of these tasks can take a couple of hours at the start of the filling run. But once you get over that hurdle, there is usually no need for touching the machine, and no requirement for human operators in the room. In most cases, you've set up the machine in a way that enable it to run for hours and hours without stopping, and really with minimal intervention.

What does the “minimal intervention” consist of?

Every hour or two, a QA technician should check vials and make sure that the lot numbers are stamping correctly, or that the fill volumes have remained within the specified limits. This is only pulling product off the production line though, no one enters the sterile filling space unless there is a machine issue, so this helps keep the microbial load low.

How long can a BFS machine reliably run in a single, continuous production batch operation?

I've seen them run 24 hours without stopping.

Beyond materials evolution, increased flexibility and speed, and aseptic filling, what other major evolutions and improvements have arrived in recent years for packaging of sterile liquids?

BFS means that more sterile liquids can be packaged with aseptic processing as opposed to terminal sterilization, which requires moving the filled and sealed containers through a closed environment, using devices called autoclaves that generate elevated temperature and pressure. I think of terminal sterilization as a kind of steam cooking procedure. For efficiency and a streamlined process, I much prefer aseptic filling. This method also allows you to fill temperature sensitive products as they don’t see the heat of a steam sterilization cycle.

Software control of the BFS fill-finish process appears to be a sophisticated operation. Can you explain how it works?

The complete BFS production cycle consists of forming a plastic container, filling it, and sealing it – and it takes three to seven seconds. During that short time, there are probably 50 parameters and functions that must be controlled in terms of time started, time stopped, sequence, and the amount of energy required for each sub-step in the cycle.

These parameters and functions include – to name just a few – support airflow rate, closing of the main mold, creation of a vacuum that pulls the parison against the mold (the hollow container shape), bringing the fill nozzle down, filling the newly formed parison with liquid, sealing the top of the container by closing the head mold, and so on.

Each of these steps requires the setting of a master field timer, individual timers, delay timers, and more. In addition, the operator must set the parameters for implementation and standardization of machine services, cleaning of product, contact services, and sterilization of the product pathway.

If you’re observing a BFS machine in operation, you probably don't even notice all of these steps occurring while the process is running. It's just a continuous flow to someone casually looking at it. But the total process is a precisely choreographed sequence of high speed actions and steps that must be performed correctly, and the instructions for the sequence and duration of each step must be accurately programmed and maintained in order for the fill-finish operations to continue properly.

All these functions are governed with a Programmable Logic Controller, or PLC. It's basically the “brain” of the BFS machine that is giving instructions to all the devices inside the machine. It constantly records data (inputs) from each step, in order to issue new instructions (outputs) accordingly. For this reason, the PLC is constantly monitoring temperatures, component positions, and various sensors while giving commands to valves, cylinders, motors, etc.

The PLC takes in that data and runs it through a logic program. Then it says, “Okay, I see that you've closed the main mold, so now you can lower the filling nozzles. Now you can inject the liquid through the nozzle, into the container...” And so forth.

In other words, the PLC is sort of a “traffic director,” if you will, but it operates on a timeframe of milliseconds. That is the magic of a high-speed manufacturing machine is that operates continuously and automatically.

For experienced pharma industry engineers and executives, who may not have witnessed the inner workings of BFS firsthand, what is the greatest challenge to understanding this technology?

It can be difficult to imagine or visualize the BFS fill-finish process based exclusively on a verbal description, until you actually see it in operation.

For example, take someone who is experienced with other materials and alternative fill-finish processes. They often think in terms of a static, fixed container that was created in an entirely different location, weeks or months before it’s filled. With this long-term, distributed process as their reference point, when they imagine BFS, they might easily say:

“Wait a minute! You have this container that's being formed from molten plastic, and at the same time it’s being filled with sterile liquid? And you’re telling me it's safe, and it’s easy for a patient to use? How could you possibly do that? It doesn't make sense.”

But when industry members see a BFS machine in operation and observe the simplicity and reliability of the process for themselves, many say: “Okay, now I get it.”

If we were to step back and summarize the big picture here for advances in sterile liquid packaging and form factors during the past few years, what's the major headline?

I would say the big news is the increased understanding and acceptance by the pharmaceutical industry of the advantages of BFS. There is a growing appreciation that BFS offers the capability to produce very high volumes of units on an accelerated timetable, and yet also to produce small runs when needed.

In addition, there is growing awareness in the industry about the advantages of aseptic fill-finish and the economical process that can be achieved with BFS manufacturing of plastic containers for sterile liquid drugs.

After years of being advocated by a select portion of the industry, BFS is really moving to the forefront, and is increasingly a big player in sterile liquid packaging.

Thank you, Jon.