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The Heat Factor: Why It Matters in Blow-Fill-Seal

Part 1 of a 2-Part Series

By JEFF PRICE
Principal BFS Engineer, ApiJect

Jeff Price has specialized in Blow-Fill-Seal technology for 28 years. As Principal Engineer at his own firm, Icon Engineering, Inc., he designed what became Rommelag's® 434 BFS rotary manufacturing machine. He also supervised BFS design, production, manufacture, test, Process Validation and more as VP of Operations and Engineering at Nephron Pharmaceuticals Corp.

Bestselling writer Victoria Aveyard once explained why heat is both a blessing and a curse in human life. She said: "The thing with heat is, no matter how cold you are, no matter how much you need warmth, it always, eventually, becomes too much."

Ms. Aveyard is right, of course. This same paradox also applies in the pharmaceutical industry, especially when it comes to packaging sterile liquids in a heat-molded plastic container. That is what happens with the advanced aseptic packaging process known as Blow-Fill-Seal, or BFS.

BFS is getting a lot of attention in the global pharma world these days. The U.S. Government has stepped up to join ApiJect in supporting its efforts to build BFS capacity for the potential packaging of tens of millions of single-unit doses of COVID-19 vaccines.

With Blow-Fill-Seal, by creating "just enough" heat, you can produce 25,000 of these plastic containers per hour, aseptically fill them with anything from vaccines to eyedrops, and then seal them, all in strips of 25 at a time, in about 3 seconds per cycle.

So when it comes to packaging vaccines in BFS injectors, heat is absolutely necessary. Yet if you create "too much" heat during this process, you risk "cooking" the full efficacy out of the Active Pharmaceutical Ingredient — much like overcooking your eggs at breakfast.

That's why heat is both a blessing, and yet potentially a curse, for packaging sterile liquids in BFS.

Fortunately, heat is a factor that Blow-Fill-Seal experts have been researching and designing around for many decades. They understand the heat-related challenges and requirements for

packaging safe, effective vaccines. And, they have developed a series of strategies — design, engineering, processing, materials handling, and environmental — to control the vital heat factor in the BFS packaging process.

The basic challenge can be defined with a couple of stark numbers. It's a question of temperature ranges. Most sterile liquid pharmaceutical products such as vaccines and medicines need to stay in the 2-8 degree Celsius range, which is 35-46 degrees Fahrenheit. (Even APIs like Pfizer's COVID-19 vaccine, which must be stored at minus 70 or minus 80 degrees Celsius — i.e., as low as minus 176 degrees Fahrenheit — can be filled at the 2-8 degree range, and then subjected to deep-freeze after filling.)

But to create a BFS container in the first place, you have to heat up the raw plastic pellets (pharmaceutical-grade resin) to roughly 180 degrees Celsius, which is 330 degrees Fahrenheit.

How can you put a sterile liquid that is 2-8 degrees into a plastic container that was formed at 180 degrees, just a second before it's filled? That, in essence, is the heat challenge for BFS pharma production. Obviously, if you fill an 8-degree liquid into a 180-degree container — and if you don't do anything to mitigate the impact of that heat differential — then the liquid's temperature is going to shoot way up, immediately.

Somehow, the BFS machine and process must control the temperature of both the newly-formed plastic container, and the sterile liquid that is poured into it.

This is not only possible; it's already being done 50 billion times a year with Blow-Fill-Seal products all over the world.

In my next post, I'll reveal how.

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How We Beat the Heat in Blow-Fill-Seal

Part 2 of a 2-Part Series

By JEFF PRICE
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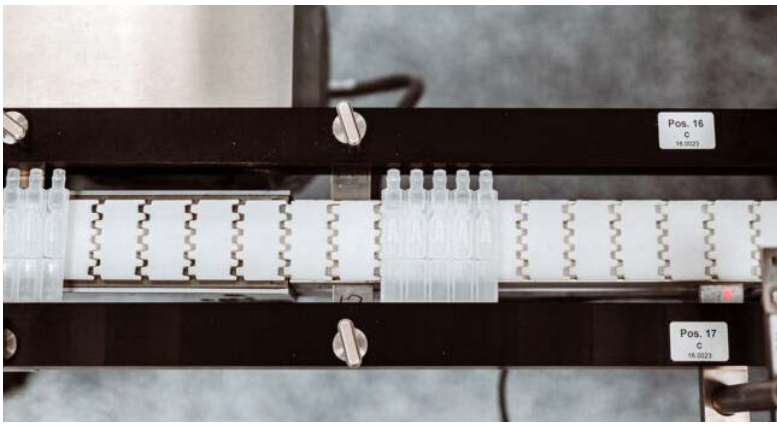
Jeff Price has specialized in Blow-Fill-Seal technology for 28 years. As Principal Engineer at his own firm, Icon Engineering, Inc., he designed what became Rommelag's® 434 BFS rotary manufacturing machine. He also supervised BFS design, production, manufacture, test, Process Validation and more as VP of Operations and Engineering at Nephron Pharmaceuticals Corp.

When you're producing a Blow-Fill-Seal (BFS) plastic container from molten resin, and filling it a second later with heat-sensitive vaccine or other sterile liquid, how do you compensate for a spread of 178 degrees Celsius between the resin and the vaccine?

That is the difference between the temperature of molten plastic as it becomes a brand-new BFS container, and the vaccine that is aseptically filled into it.



For example, let's say the drug product must remain between 2-8 degrees Celsius in order to retain and ensure its potency and efficacy. Yet the resin must be heated up to 180 degrees in order to be extruded by a BFS machine into a tube, known as a parison, that will contain that vaccine.

As an analytical engineer, I've been working on this question since 1997. Working with a NASA consultant company that specialized in thermodynamic modeling, we came up with 19 related variables that together determined the heat of the liquid contents that were filled into a BFS container as it was being formed and sealed.

The results of that work were presented at the BFS Operators Association in 1998 in Boston, Massachusetts.

To start with, although the molten resin is heated to 180 degrees Celsius, the resulting container is roughly 110 degrees by the time the liquid content begins flowing into it. Our model showed that the first drop of liquid to enter the container, naturally, experienced the greatest spike in temperature. The second drop had less of a spike, and the third drop still less, and so on, because of various

factors that were cooling both the container and the liquid. (Keep in mind, it's a very rapid operation; the entire BFS filling step takes less than a half-second for a 0.6ml fill.)

The strategy to keep the API cool is to offset the heat of the plastic, so that the liquid contents don't wind up absorbing all that heat. There are several strategies to do this, some inherent to BFS technology and some particular to molds and container designs.

I'm glad to say that at ApiJect, we employ a number of these strategies. These include, among others:

(1) The molds are kept relatively cool, around 40 degrees Celsius depending on the type of container. This is done by running very cold liquids inside the molds just before they are used. That reduces the temperature of the plastic parison, i.e., the container that is being formed, to about 110 degrees prior to filling.

(2) ApiJect's container design results in very thin plastic walls. That's sturdy enough to be robust for shipping and use at the point of care, but thin enough so that it does not provide a lot of unnecessary plastic which can absorb and trap more heat.

(3) ApiJect super-cools the liquid vaccine or medicine down to 8 degrees or even 5 degrees Celsius, just before we fill it into the container.

(4) ApiJect fills the liquid into a single small chamber of the container, so it doesn't have to "fight against" all the heat that is stored (for the moment) in the entire BFS container.

By deploying these strategies, the BFS fill and finish operation can be controlled to ensure that, in this scenario, the hot plastic and the cool liquid do not exceed a temperature of about 30 degrees Celsius. That's assuming half a milliliter of liquid is being filled, which is a standard vaccine dose amount.

Long ago, U.S. President Harry Truman famously said: "If you can't stand the heat, get out of the kitchen." But in the world of BFS we say, "If you want to beat the heat, design a better kitchen!"

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