

Critical Thinking

Sterile blow-fill-seal (B/F/S) users need to develop a formal capability study on the critical processes of their aseptic B/F/S filling operations, while ensuring that adequate controls are in place to satisfy an inspection from the FDA or other regulatory authorities

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Aseptic blow-fill-seal systems for filling of pharmaceutical liquids provide a unique combination of flexibility in packaging design with unparalleled sterility assurance. B/F/S pyrogen-free moulding of containers and ampoules for injectables, ophthalmics, biologicals and vaccines have received international acceptance as suitable for pharmaceutical liquids applications, capable of delivering precise dosing in disposable formats.

Temperature-sensitive biological and protein-based products can be processed in advanced B/F/S machines,

and such systems also allow single-dose container packaging, frequent changeover for short production runs, and the capability to incorporate pre-moulded, pre-sterilised components (inserts) into the basic container; items such as rubber and silicone stoppers and tip-and-cap dropper units for eye drop containers. These benefits are continuing to push the acceptance and use of advanced aseptic B/F/S technology to the forefront of the pharmaceutical industry. For these reasons, B/F/S systems have been recognised by the U.S. Food and Drug Administration as an advanced aseptic process, indicating

it as a preferred technology over other aseptic systems.

B/F/S Process Validation and Advanced Technology

Although highly capable of producing enhanced sterility assurance levels, B/F/S has been closely inspected by regulatory agencies around the world, primarily due to the complex nature in which sterile, highly reproducible results are achieved when using B/F/S systems. Due to the complexity of its technology, B/F/S requires sufficient process validation to ensure the regulatory environment has

Figure 1: Optimum critical process parameters in aseptic BFS enable unique precision features like top geometrics and engraving



Images: Weiler Engineering, Inc

adequate data to support approval of long-term production.

Such B/F/S systems are automated extensively, and designed to require minimum human access and reduce risk to the product's integrity, while operating in a classified environment. Various in-process control parameters, such as container weight, fill weight, wall thickness and visual defects, provide information that is monitored and facilitates ongoing process control. Its containers are formed from a thermoplastic granulate, filled with a liquid pharmaceutical product and then sealed in a continuous, integrated and totally automated sequence – the critical fill-zone area is shrouded under a continuous flow of positive-pressure sterile filtered air. The B/F/S cycle is thus completed within seconds.

The most advanced aseptic blow-fill-seal machines use a modular design integrating a class 100 environment for filling and manufacturing processes, while utilising servo-drive motors to perform precision motions through system-integrated programmable logic controllers (PLCs). The PLC receives continuous communication from the B/F/S system, continually monitoring process times, temperatures, differential air pressure, and ensuring that non-viable particle counts are within range inside the class 100 environment.

Additionally, the PLC can maintain recipes for the different machine process parameters required to run different liquid formulations and product configurations. These advanced B/F/S systems address process monitoring, streamlined maintenance and consolidated machine components for optimum performance.

Due to the high level of automation, advanced B/F/S machines require minimal intervention during normal operation, provided that the machine has been properly adjusted and stabilised at start-up. Mechanical and electrical settings are fixed and secured during the initial setup to avoid variations in processing. On-site adjustments and set-points of timers and speed controls, such as to accommodate environmental or batch requirements, can be done via remote human machine

interface (HMI) terminals located outside of the clean room.

Evaluating Critical B/F/S Process Parameters for Quality and Sterility

From an FDA or other regulatory agency standpoint, the expected requirement would be a complete understanding of an in-control process, achieved with a machine design that can produce a high-quality product in a reliable and qualified manner. This is what a critical process parameter study would need to achieve.

The objective of any process parameter study is to develop and differentiate the process parameters from the critical process parameters, and learn how these parameters will affect the process when pushed to the edge of failure. From this data, optimum parameters should be developed that can be used to execute future process validations.

Critical processing parameters are a subset of overall process parameters for the entire machine cycle. Critical process parameters in B/F/S consist of two categories: quality attribute processing parameters and sterility related processing parameters.

Key to this process is maintaining quality output whilst also ensuring consistent production volume. Critical quality attribute process parameter ranges can successfully be put into place without inhibiting the ability to functionally operate the equipment at high quality standards and at high efficiency levels. This typically means maintaining batch yields with reject rates of approximately one per cent or less.

A company would need to develop what its critical processing parameters are in relation to quality attributes. Every vial and bottle configuration needs to have established the timers that will have a direct effect on the formation of each of these vials and bottles.

Relative to sterility related process parameters, improved sterility and minimising particulate matter are two of the most critical requirements for manufacturing aseptically-produced

products, and more recently advanced B/F/S technology has provided distinct advantages over earlier B/F/S systems. These include controlling the air pressure cascade in the nozzle shroud by employing HEPA air showers to assure a class 100 environment under dynamic filling conditions. Improvements such as this have enhanced sterility assurance, and thereby, improved regulatory compliance.

During aseptic processing using B/F/S technology, the only opportunity for product contamination occurs while the container is open to the environment prior to sealing. This time is identified as the critical process time. The duration of the critical process time is controlled by the sum of a number of sterility critical machine process (timer) parameters.

As a worst case scenario, when performing media fills the sum of the critical process time parameters needs to be greater than the sum during a normal production run. This will ensure that the limits of process capability are adequately tested to the environment and the process in general.

A company should develop its own machine parameter set-up sheet that adequately addresses its business needs and QA/QC requirements. The set-up sheet requires accurate development to establish minimum, maximum and actual set-points for each of these parameters. This will provide the B/F/S operator with the information necessary to stay within an acceptable range as previously determined from these engineering studies. The machine parameter set-up sheet should incorporate a table to document any changes to the critical process time parameters during production. This form can be easily incorporated into a batch record or used as a standalone form maintained by engineering, maintenance or any other department deemed responsible.

The following database of machine critical processing parameters will be a useful tool in diagnosing plant and machine related issues, resulting in more efficient and controlled processes, with the facility to produce quality products in the shortest amount of time.

Quality Attribute Critical Process Parameters for Main Mould Vacuum Delay Vials

This timer is used to form the main body of the vial once the mould has closed on the parisons. As soon as the mould is closed, the timer is activated for a specified period before the vacuum solenoid is energized, to pull the molten plastic into the mould cavity to form the vial, before filling. The timer is typically run at 0 to 0.15 seconds.

When it comes to producing bottles the timer is used in conjunction with the blowing timer to ensure that adequate formation of the main body of the bottle is successfully achieved. The premise of operation for the main mould vacuum delay timer for a bottle is identical to a vial; except with a bottle, the main mould vacuum delay timer is typically much longer. The lengthy delay for a LVP is primarily due to the time it takes for the main mould carriage to reach the forward position under the class 100 nozzle shroud. This timer is typically run at 1 to 1.50 seconds.

Bottle Blowing Timer

This timer is used in conjunction with the main mould timer for both large volume parenteral (LVP) and small volume parenteral (SVP) bottles, typically when polypropylene is the resin of choice. Through high pressure air, a solenoid valve is energised open to allow a free flow of air through a sterilising filter into the vial or bottle. Once energised the bottle blowing timer will remain open as per the PLC controlled machine timer set-point. This timer is critical because many times for LVPs the parison wall thickness is quite thick and vacuum alone would not be able to pull the plastic into the deep walls of the main mould cavities. It is also critical to ensure that any engraving on the vials be completely filled with molten plastic to create defined depressions on the body of the vial or bottle once the product is released from the mould. This timer is typically run at 0.25 to 3.00 seconds. The longer time for an LVP product, the shorter timer for an SVP product.

Seal Mould Vacuum Delay

This timer is used to form the seal mould area, which includes the twist-off portion for product dispensing or the dome portion for cap welding. This timer is also critical to the formation of the cosmetic portion of the vial or bottle where any engraving is located for product or company identification. This timer is activated as soon as the seal moulds start to close. General settings range from 0.00 to 0.25 seconds.

Sterility Related Critical Process Parameters

All sterility related critical process parameters need to be proven and tested as part of a company's media fill procedures. The critical process time is viewed as the total amount of time that the parison is open during vial formation and filling. It is comprised of the sum of the following sterility related timers:

Fill Nozzle Down Delay

A delay time, which if needed, keeps the fill system in the up position before lowering into the main mould for filling. Typical settings for this timer are 0 to 0.15 seconds with no established edge of failure range at the high end.

Bottle Blowing Timer

The timer which energises a solenoid valve to the open position and allows high-pressure, sterile air to enter into the vial or bottle for a specified period of time. Typical settings for this timer are 0.25 to 3.00 seconds.

Bottle Vent Timer

The timer which allows the high-pressure air that was blown into the vial or bottle to be evacuated out to the vial/bottle prior to filling. Typical settings for this timer are 0.10 to 1.50 seconds, dependent on bottle geometry and internal volume.

Master Fill Timer

The timer which actuates all fill solenoids for the same amount of time. This timer is adjusted if all vials/bottles need to be adjusted higher or lower for fill volume across all cavities.

Individual Fill Timer

These timers would be adjusted individually based on the mechanical response and flow rate should any one vial or bottle need adjusting higher or lower to reach the target.

Fill Nozzle Up Delay

After a complete filling cycle, this timer is activated to provide a delay before the fill system starts its travel to the up position. Typical settings for this timer are 0 to 0.15 seconds.

Implementation

It is important to provide detailed results on these critical process parameters based on only cause and effect observations. Once the parameters are determined, each timer needs to be adjusted up or down to achieve the edge of failure on both sides of the range. The conclusion to any critical process parameter development needs to incorporate clear and concise direction as to the study findings and results. These results should then be inserted as part of the firm's process parameter development protocol.

With this protocol in place, aseptic blow-fill-seal systems will continue to produce sterile pharmaceutical liquid products that meet the mandates of government regulators, and provide pharmaceutical manufacturers with the most cost-efficient aseptic packaging systems while maintaining product integrity.

About the author



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