Improving Uptime in Aseptic Processing of Pharmaceutical Liquids with Blow-Fill-Seal

Maximized uptime, minimized changeover time and efficient OEE are key factors that have influenced the acceptance of aseptic blow-fill-seal in the packaging of pharmaceutical liquids.

by Chuck Reed, B.Sc/MS
Director, Sales & Marketing, Weiler Engineering, Inc.

Pharmaceutical manufacturers, for many years, have experienced exceptional growth with the development of new drugs and the marketing of these products, but pharmaceutical manufacturing processes have historically lagged behind in efficiency compared to those of other consumer product industries. Within the past decade, however, responding to changes in consumer purchasing such as the influence of the Internet, stiffer guidelines from the Food and Drug Administration and other regulatory agencies, and significantly increased costs to bring new drugs to market, drug companies have had to take a closer look at their manufacturing processes to make them more efficient, to stay competitive.

A key factor to reaching high levels of efficiency in pharmaceutical manufacturing is maintaining uptime, which has always been of critical importance to manufacturers in every industry. When throughput is interrupted, or not running because of downtime or changeovers, the entire process line is affected, which can present a significant production loss to the pharmaceutical manufacturer.

Overall Equipment Effectiveness

An important tool that pharmaceutical manufacturers are using to increase uptime, and measure and improve line efficiency is Overall Equipment Effectiveness (OEE). OEE measurement is also frequently used as a key performance indicator (KPI) in conjunction with lean manufacturing efforts to provide an indicator of success.

Overall Equipment Effectiveness (OEE) is a system of analytics to determine how effectively a manufacturing operation is utilized. It identifies and quantifies the performance of specific areas of a manufacturing line to bring about process improvement. OEE is determined by factoring three key metrics of machine and line operation: 1) availability; 2) performance; and 3) product quality.

Availability represents the percentage of scheduled time that the process is available to operate. Also referred to as uptime. Factors like equipment cleaning, changeovers, equipment breakdown and preventative maintenance are conditions that will influence the OEE metric rating for Availability.

Performance represents the speed at which the process or machine runs as a percentage of its designed speed. Factors that influence the OEE rating for Performance include temporary equipment stops from jams, machine cycle settings, designated speed and product throughput.

Quality in the OEE metric represents the good products produced as a percentage of the total units started. This OEE rating is influenced by rejected products. More specifically, those rejects caused by equipment or personnel, and those rejects separated into rework and scrap.

Each of these metrics are then factored at a percentage of operation compared to the ideal operating condition. For example, a given line may have an Availability factor of 86.7

percent, a Performance rating of 93.0 percent, and a Quality factor of 95.0 percent. The OEE would then be computed by multiplying 86.7% x 93.0% x 95.0%, for a composite OEE metric of 76.6 percent for that line.

Typically, each metric would factor in many pieces of equipment and operating aspects of the pharmaceutical line to arrive at a percentage. In pharmaceutical packaging these machines may include sorters, fillers, cappers, labelers, cartoners, case packers and palletizers. Each machine would have its own systems and cycles. An OEE rating can be determined for each machine on the line, and/or for the entire line.

Blow-Fill-Seal Processing of Aseptic Pharmaceutical Liquids

One area of pharmaceutical manufacturing that has made significant gains in Overall Equipment Effectiveness is in the packaging of aseptic pharmaceutical liquids with blow-fill-seal (B/F/S) technology. From the perspective of OEE, and focusing on uptime and changeover time improvement, aseptic blow-fill-seal machines present highly efficient systems for production of sterile liquid products.

The aseptic blow-fill-seal system has proven to improve product integrity and better ensure patient safety over traditional aseptic processing procedure. As a result, the United States Food and Drug Administration and the United States Pharmacopoeia now characterize modern B/F/S technology as an 'advanced aseptic process', indicating its use as a preferred technology over other aseptic systems, and a better solution for the sterile, aseptic processing of pharmaceutical liquids.

B/F/S is a self-contained process. The consolidation of process steps results in streamlined efficiency for the entire liquid filling and packaging production process. The technology integrates a three-step process of blow molding, sterile filling and hermetic sealing in a continuous, highly-automated operation. Unique to aseptic B/F/S systems

compared to traditional aseptic processing is their capability for rapid container closure and minimized aseptic interventions. Further, B/F/S incorporates the use of recyclable plastic resins. Low-density polyethylene, high-density polyethylene and polypropylene, used to produce aseptic containers for injectables, ophthalmics, biologicals and vaccines are generally considered inert by the FDA.

Simplified B/F/S Machine Design Improves Uptime

Traditional aseptic procedures for packaging pharmaceutical liquids involve multiple steps in the handling and manipulation of the material, containers and sterilization filling processes with human intervention, and therefore have a heightened potential for system downtime and product contamination during processing. Manual processing steps for conventional aseptic processing include receiving, inspection and warehousing of incoming containers, washing and sterilizing of containers, separate processing steps and equipment for filling and sealing, and end processing handling such as labeling.

In pharmaceutical processing, it is the filling process that determines the line speed. System delays and downtime caused by such manually-dependent processes in aseptic packaging can have significant throughput and cost consequences which depress OEE.

Conversely, automating the aseptic process can have a sizable impact on improving uptime. The most advanced aseptic B/F/S systems are quite automated, compared to traditional aseptic processing. These B/F/S machines are designed to require minimum human access while operating in Class-100 environments. Various in-process control parameters utilizing the latest generation of fully-system-integrated PLCs, control and monitor container weight, fill weight, wall thickness, isolation of visual defects and other factors, facilitating optimized system function.

With the latest generation of blow-fill-seal machines, as exemplified in the ASEP-TECH® B/F/S system from Weiler Engineering, the forming, filling and sealing

steps are achieved in one unit operation—the cycle being completed within seconds. Such automation eliminates unneeded manpower and reduces the risk to product integrity. These B/F/S machines allow very efficient processing speed and short machine cycle times. They minimize the time required to perform complex tasks and increase efficiency in process operations. Such automated process technologies improve product quality and consistency, and increase production throughput, substantially supporting Overall Equipment Effectiveness.

Flexibility of B/F/S Container Design Optimizes Machine Operation

B/F/S allows considerable flexibility in the design of containers, adding to improved OEE. Pre-molded, pre-sterilized components, called inserts, can be easily integrated into the basic container. These inserts, including items such as rubber and silicone stoppers, and tip-and-cap dropper units for eye drop containers used to deliver a calibrated drop, are attached to the container after the blowing and filling process, prior to sealing. These improvements streamline the packaging process, eliminating the need for secondary packaging. Labeling is not needed, since the molds can be engraved with product information, which avoids an additional process step.

Advanced aseptic B/F/S containers and ampoules can be manufactured to deliver precise dosing in disposable formats. The incorporation of a sterile tip-and-cap, a rubber stopper or a multi-entry insert into the B/F/S package offers added flexibility in container design and drug delivery methods, as well as enhanced sterility safety.

Quick Changeovers

Packaging equipment changeovers present one of the most costly and time-consuming activities within pharmaceutical manufacturing. Indeed, changeover adaptability remains the most critical packaging machine feature, with sizable influence on OEE. The versatility of packaging equipment to facilitate rapid changeovers has never been more important in pharmaceutical manufacturing, and aseptic blow-fill-seal systems exemplify this initiative.

Many B/F/S machines are configured to produce more than one bottle shape or format. This makes it easy to change over from one container size to another. A B/F/S machine might produce a family of 2ml, 3ml and 5ml containers, then switch to a family of 5ml, 10ml and 15ml containers, or to one of 10ml, 15ml and 20ml containers, moving from one to the other with relative ease of machine set-up. This is ideal for manufacturers, such as those performing contract packaging of aseptic liquid pharmaceutical solutions, because of their need for changeover flexibility. ASEP-TECH® B/F/S systems from Weiler are capable of producing containers ranging in size from 0.1ml to 1,000ml at production rates of 15,000 units per hour, depending on container configuration.

The growing usage of biologics is demanding packaging in different formats. These drug products usually require smaller process runs and are typically heat sensitive. Many of these new biotechnological drugs do not withstand terminal sterilization with steam or irradiation, and so are best treated aseptically. More advanced B/F/S machines are designed so they can handle these heat sensitive products without adversely affecting product quality.

The B/F/S process offers outstanding versatility for multiple container designs. A unique design feature offered on the ASEP-TECH® B/F/S systems, for example, permits the insertion of a secondary delivery device into the container prior to the final hermetic sealing step. This feature can be suspended, however, without requiring significant equipment changeover. This allows the production of standard containers without inserts on the same machine with only a simple recipe and tooling change.

To further minimize potentials of system downtime, some pharmaceutical manufacturers are now segmenting their high-volume aseptic process lines into multiple, smaller blow-fill-seal lines. The use of smaller machines provides enhanced production flexibility and improved efficiency. In the event that one of the lines goes down for maintenance or repair, it will not stop the entire production throughput. Products can be easily ‘campaigned’ with B/F/S, using one line with one container geometry for multiple

products. Since B/F/S is ideally suited for these 'campaigns' due to quick changeovers, it is a natural pick for manufacturers desiring to optimize OEE.

Efficient Utilization of Time

Modern B/F/S system design embodies OEE initiatives, being focused on changeover simplicity and flexibility, and permitting shorter runs, increased uptime and maximized throughput.

Blow-fill-seal machine efficiency rates very high. More advanced blow-fill-seal machines can approach 99 percent uptime efficiency, significantly higher than traditional aseptic processing, which is plagued with slow-downs, in part because of manual interventions. B/F/S also performs noticeably higher than the peak 70 percent operating efficiency of the world's most streamlined pharmaceutical manufacturing facilities.

Improved uptime, minimized changeover time and efficient OEE are key factors that have influenced the acceptance of aseptic blow-fill-seal. These are critical functions for achieving improved product quality and profitability in the packaging of aseptic pharmaceutical liquids.

About Weiler Engineering:

Weiler Engineering is a worldwide provider of aseptic blow-fill-seal custom packaging machinery for pharmaceutical and healthcare applications. Based in Elgin, Illinois, and founded in 1959, Weiler's proprietary blow-fill-seal system is the culmination of 40 years of innovation in machine design and sterile process development, producing a highly advanced aseptic liquid packaging system. Its ASEP-TECH® blow-fill-seal technology integrates blow molding, sterile filling and hermetic sealing in one continuous operation to produce aseptically manufactured products.

The company uses the latest technological advances in equipment design and systems to ensure the highest level of quality in the production of sterile liquid products. Its equipment must meet demanding corporate, scientific, regulatory and end-user requirements. These application challenges are met through the offering of several machine models designed to manufacture containers ranging in size from 0.1 ml to 1,000 ml at production rates of up to 15,000 units per hour, depending on container configuration.

To reach Weiler Engineering, please contact Chuck Reed; 1395 Gateway Drive, Elgin, Illinois 60124; Phone 847-697-4900; email solutions@weilerengineering.com; www.weilerengineering.com

###

Chuck Reed has extensive experience in specialized equipment design and manufacture, process technology and pilot plant design and construction. He is a member of both PDA and ISPE, is currently Chairman of the ISPE Packaging Community of Practice and is an author for the ISPE Packaging, Labeling and Warehousing (PACLAW) Baseline Guide. Mr. Reed holds a Bachelor of Science in Chemical Engineering from Clarkson University and a Master of Science in Management from National Louis University.