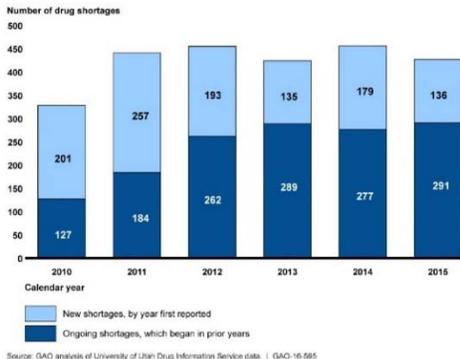


A Solution for Aseptic Syringe Filling

By ESS Technologies, Inc. Blacksburg, VA

Introduction

Many factors contribute to the need to optimize the production of pre-filled syringes. Pre-filled syringe technology simplifies the dosing and administration of a wide range of medications, from vaccines, epinephrine and insulin injections to customized treatment for a number of chronic illnessesⁱ. As the population ages, pharmaceutical manufacturers see an increase in their production requirements for parenteral drugs. However, shortages of these drugs have become more prevalent. According to a 2016 study conducted by the US Government Accounting Office (GAO):



Drug Shortages 2010-2015

Shortages of sterile injectable anti-infective and cardiovascular drugs in 2012, 2013, and 2014 were strongly associated with certain factors GAO examined. Two factors—a decline in the number of suppliers and failure of at least one establishment making a drug to comply with manufacturing standards resulting in a warning letter—suggest that shortages may be triggered by supply disruptions.ⁱⁱ

The long-term impact of failing to comply with manufacturing standards can further exacerbate the drug shortage.

Manufacturers may choose to temporarily shut down production to correct the conditions that led to the violations of current good manufacturing practice regulations cited in a warning letter. They may also shut down permanently if the costs of correcting the problematic conditions outweigh the potential benefits of producing drugs at that establishment.ⁱⁱⁱ



Filling Station on Model SF20 TaskMate® Aseptic Syringe Filler and Capper

For manufacturers who do comply with manufacturing standards, filling syringes in an aseptic process brings them unique dilemmas. “Additionally, aseptic processing of parenterals involves challenges such as protecting the sterility of a product as it moves through each phase of formulation, filtering, filling, and packaging.”^{iv} Aseptic syringe filling systems such as ESS Technologies Model SF20 TaskMate® Aseptic Robotic Syringe Filler and Capper address the dual concerns of parenteral CMOs and compounding pharmacies: increase production capacity while maintaining high manufacturing

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ISO classification number (N)	Maximum concentration limits (particulates/m ³ of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with equation (1) in 3.2)					
	0.1 μm	0.2 μm	0.3 μm	0.5 μm	1 μm	5 μm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1,000	237	102	35	8	
ISO Class 4	10,000	2,370	1,020	352	83	
ISO Class 5	100,000	23,700	10,200	3,520	832	29
ISO Class 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO Class 7				352,000	83,200	2,930
ISO Class 8				3,520,000	832,000	29,300
ISO Class 9				35,200,000	8,320,000	293,000

NOTE: Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level.

Selective airborne particulate standards classes for cleanrooms and clean zones. Classification Parameters from ISO 14644-1.

ISO Cleanroom Classifications

(Source: Moldenhauer, Jeanne. "Understanding Cleanroom Classifications," *Controlled Environments Magazine*, March 2014)



RABS with Open Top Will Be Integrated with Ventilation System



Fully Enclosed RABS

standards to ensure product sterility. This allows manufacturers to minimize drug shortages and increase the quality of health for many.

Overview of Standard vs. Aseptic Filling Machines

Standard filler/capper machines, such as ESS's MB Series Monoblock Filler/Cappers, offer pharmaceutical manufacturers a reliable process for filling and capping bottles, jars, tubes and vials while providing a high quality of manufacturing standards. Features such as ionized air blasts, nitrogen purges before or after the filling process, and the incorporation of both stainless-steel change parts that can be autoclaved and disposable tubing further increase the sterility of the packaging process. Located in an ISO-compliant "clean room," monoblock-type filler/capper machines specifically designed to meet aseptic guidelines can be used for aseptic filling, but under normal production environments, this type of equipment will not suffice.

Aseptic filling, as noted earlier, involves bringing together previously sterilized components: product, syringe, and cap, and combining them in a sterile environment to avoid product contamination. "For example, glass containers are subjected to dry heat; rubber closures are subjected to moist heat; and liquid dosage forms are subjected to filtration."^v All the components must then be kept sterile throughout the filling and capping process. Locating the equipment in an ISO-compliant clean room will meet aseptic manufacturing best practices. "ISO 14644-1, *Cleanrooms and associated controlled environments-Part 1: Certification of Air Cleanliness document*," was formally issued in 1999. This document establishes the certification requirements for air cleanliness areas. This document has replaced the old Federal Standard 209-e (Class 100, 10,000 and 100,000 designations)."^{vi}

Cleanrooms simplify the process of providing an aseptic environment, but they are expensive to build and they require significant, valuable factory floor space by limiting the processes that can be conducted in that cleanroom area. (For example, processes that may create corrugate particles and dust, such as case packing or palletizing, are ill-suited for cleanroom environments.) Restricted Access Barrier Systems (RABS) offer a good option for aseptic applications so long as they are specifically designed for aseptic applications and integrated into the production room. These systems attach to air handling systems and enclose the filling and capping equipment on all sides and above the machinery to prevent airborne contaminants from entering the filling and capping process. Glove ports on both sides of the RABS allow the machine operator to handle

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Bag of Sterile Syringes Connected to RTP



Robotic Flexible Feeding System for Syringes



Filled Syringe

the components without directly touching them, and a rapid transfer port (RTP) allows sterile syringes to be fed to the filling system without compromising their cleanliness.

Robotic Aseptic Syringe Filling and Capping

Robotic aseptic syringe filler / capper machines, such as the ESS Model SF20, integrate clean-class robots to handle the components within the filling system. The operator connects a sterile bag of drug product to the filling system through a stainless-steel access port and connects a sterile bag of syringes to the rapid transfer port. A tilt tray allows the operator to tilt syringes into the SF20's syringe hopper, which transfers the syringes to a vibratory tray of the robotic flexible feeding system. Cap tray drawers with removable protective guarding allow the operator to load trays of sterile syringe caps in the system.

A FANUC six-axis, clean-class robot with iRVision locates syringes on the backlit vibratory tray and picks one using specially designed vacuum-style end-of-arm tooling (EOAT). The robot orients the syringe and places it on the filling station. A precise amount of drug product is dispensed, bottom-up, into the syringe. Net weigh cells may be incorporated into the filling system to verify the fill accuracy. As the syringe is filled, a second FANUC clean-class robot with custom, multi-function EOAT picks a cap and places it in the capping chuck. A stainless steel, servo-driven pick-and-place arm moves the filled syringe from the filling station to the capping station. After the cap torque is applied, the capping robot picks the filled and capped syringe and drops into a stainless-steel discharge chute or reject chute (for non-compliant fills or caps).

Advantages of Robotic Filler/Capper Systems

A robotic solution offers a number of advantages to pharmaceutical manufacturers. FANUC clean class robots meet ISO Class 4 (old Class 10) cleanliness standards with epoxy paint, an antirust surface, and food grade grease.^{vii} The robot EOAT attaches with quick release connections, allowing the operator to perform a product changeover in a matter of minutes. The EOAT can also be upgraded in the future to handle additional syringe sizes. Robotic motion is consistent and reliable, allowing the automated system to fill and cap up to fifteen (15) syringes per minute, depending on the required fill levels.

FANUC robots are the most reliable in the world. More than 450,000 installations worldwide allow for statistical analysis proving 100,000 hours mean-time-between-failure.^{viii} Robots suffer from none of our human foibles such as fatigue, repetitive motion injuries,

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Trays of Caps



Capping Station and Discharge / Reject Chutes

or distractions, allowing them to function consistently and with a maximum rate of productivity at all times. In addition, robots cannot be injured or sickened by mishandling syringes or exposure to the drugs.

Conclusion

To address drug shortages, manufacturers of parenteral pharmaceuticals need a reliable, high quality means of producing sterile syringes in an aseptic environment. While clean rooms provide such an environment, they are expensive and require significant floor space. Stand-alone robotic syringe filling and capping systems integrated with Restricted Access Barrier Systems (RABS) create a compact aseptic solution for manufacturing syringes at rates up to fifteen syringes per minute. Designed to meet FDA pharmaceutical manufacturing best practices, robotic syringe filling and capping systems allow manufacturers to increase productivity while maintaining high product quality. Robots allow the operator to stay outside of the sterile area, protecting valuable human resources from exposure to potentially harmful agents as well as preserving the quality of the drug being manufactured.

ⁱ “Prefilled Syringes & Parenteral Contract Manufacturing: Biologics Present a New Set of Challenges,” *Drug Development and Delivery Magazine*, May 2016, second paragraph. Accessed 2/23/2018. (<http://www.drug-dev.com/Main/Back-Issues/SPECIAL-FEATURE-Prefilled-Syringes-Parenteral-Cont-1114.aspx>)

ⁱⁱ US Government Accounting Office, “Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge” (Report # GAO-16-595) July 7, 2016, highlights of the report. Accessed 2/7/2018. (<https://www.gao.gov/assets/680/678281.pdf>)

ⁱⁱⁱ Ibid.

^{iv} “Prefilled Syringes & Parenteral Contract Manufacturing: Biologics Present a New Set of Challenges,” *Drug Development and Delivery Magazine*, May 2016, fifth paragraph.

^v US Food and Drug Administration “Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice” September 2004, page 3. Accessed 2/6/2017. (<https://www.gao.gov/assets/680/678281.pdf>)

^{vi} Moldenhauer, Jeanne. “Understanding Cleanroom Classifications,” *Controlled Environments Magazine*, March 2014, ninth paragraph. Accessed 2/23/2018. (<https://www.cemag.us/article/2014/03/understanding-cleanroom-classifications>)

^{vii} FANUC America Product Brochure, “LR Mate 200iD.” 2013, page 2. Accessed 3/1/2018. (http://www.fanucamerica.com/cmsmedia/datasheets/LR_20Mate_20200iD_20Series_187.pdf)

^{viii} ESS Technologies. “FANUC Robotics Training and Support.” (<http://www.esstechnologies.com/Training-Support.shtml>).