

STERILINE COMPLETES INSTALLATION OF A STATE-OF-THE-ART FULLY AUTOMATED ISOLATOR BASED FILLING LINE FOR BERKSHIRE STERILE MANUFACTURING WORKING WITH FIVE COMPANIES

A five-player effort to integrate a fill/finish solution for glassware in bulk and tubs with lyophilization capability

Innovation at BSM continues

Steriline, an Italian manufacturer of both robotic and standard fill/finish lines for aseptic processing of injectable drugs, has recently delivered a line to process syringes, cartridges and vials both in bulk and in ready to use (RTU) tubs to **Berkshire Sterile Manufacturing (BSM)**.

Located in Lee, Massachusetts; BSM is an American contract manufacturing and development organization (CDMO) performing filling and packaging of injectable drugs for the pharmaceutical and biotech industry, with a focus on small-scale and clinical manufacturing.

With the mission of providing the safest sterile drug products for clinical use and small-scale requirements achievable, BSM has consistently grown, thanks to the far-sighted vision of its founders, two industry experts in sterile drug manufacturing. Today, BSM employs over 200 people and provides sterile filling and development services for vials, cartridges, and syringes in batch sizes up to 60,000 units.

The facility has a current filling production range from 2mL to 100mL in glass vials (bulk or RTU), 0.5mL to 10mL in glass or polymer syringes, and up to 3mL in glass or polymer cartridges. Product in glass vials can be closed in liquid form or lyophilized (freeze dried).

In 2021, BSM invested an additional \$20 million to expand its production capacity and capabilities. The investment included additional laboratory and warehouse space and doubled their cleanroom facilities to prepare for a new, **fully automated, 100% isolator-based, flexible sterile filling line with a freeze dryer**.

BSM requested that the filling line have the capacity for 60,000-unit batches of either vials (bulk and RTU), syringes, and cartridges with lyophilization capability up to 35,000-unit batches for 10R vials, including a RTU tub active decontamination system. Initially, BSM evaluated local partners and commissioned a filling machine from Colanar, a capping machine from Genesis, and a freeze dryer from IMA. Finally, Steriline was asked to provide the complementary machines and isolators and a Robotic Tub Decontamination System (RTDS2) for RTU tubs by UV built by Claranor to complete the line and incorporate all the equipment in a unique, turn-key design.



Fig. 1 – The sterile filling line delivered to BSM

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Steriline, as primary supplier of the project, provided the following machines:

- RA-V4 - **Rotary Washing Machine**
- VP300 - Vial Pusher Loading System
- ST0-CCS - **Depyrogenation Tunnel**
- RT600 - Rotating Table (linked to a Linear Belt Transfer (LBT))
- SDB - Semi-Automatic Debagging Machine under oRABS
- RTDS2 - **Robotic Tub Decontamination System**
- ADE - Automatic Robotic Delid/Deliner Machine under Isolator
- ISO - **Filling Machine Isolator**
- PDS - Positive Diverting System
- LAF - Laminar Air Flow System for the Lyophilizer Loader/Unloader
- oRABS - Open Restricted Access Barrier System for the Capper.

The five providers joined forces and worked together for the first time to deliver the solution by 2022.

Since the line was required to handle glass containers in both bulk and RTU tubs, flexibility was one of the main features of the deliverable as the two product presentations require different steps for the primary packaging process.

Processing glassware in RTU tubs (in a step-by-step process flow)

Glassware (vials, syringes or cartridges) in an RTU format arrive nested in thermoformed plastic tubs and are sealed with a liner and Tyvek barrier lid. The tubs are double bagged and placed in cartons, and palletized. A technician manually unpacks and removes the secondary bag then loads the bagged tub onto a belt that slides to the Semi-Automatic Debagging (SDB) station where the primary bag is removed. The SDB system is situated in a Restricted Area Barrier System (RABs).

Tubs are then positioned at the entrance station of the RTDS2. This 3-chamber decontamination system is the first machine adopting Pulsed Light Technology (PLT) for



Fig. 2 – The line for processing glassware in RTU tubs

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RTU tubs. The tub enters through the **inlet chamber**, where a robotic arm grips the tub to expose each side of the tub to four xenon lamps (by Claranor) to deliver a series of intense 0.3 ms white light flashes at 1 MW, providing sufficient power to completely decontaminate the surfaces of the tub. The system is fitted with a generator that stores energy in a capacitor, and when triggered, a pulse of 20 kV and 300 J ignites the xenon lamps that emit pulsed broad-spectrum UV light flashes that are 50,000 times more intensive than the light our Sun shines on Earth in a similar surface area. This destroys any microorganisms on the surfaces of the RTU tub prior to entering the filling line. PLT offers a highly efficient, effective, and safe sanitization without harming the packaging.

Since PLT is not effective in shadow, the RTDS2 robotic arm rotates the tub to expose all the tub surfaces to the Pulsed Light lamps ensuring that all surfaces are properly exposed and decontaminated.

Passing through the **outlet chamber**, the tub is expelled into the ADE under unidirectional airflow where a robotic arm removes the Tyvek barrier lid and transfers the tub into the filling machine. After the containers are filled and stoppered, vials can be moved into the freeze dryer (in the case of products requiring lyophilization) or directly into the capping machine to complete the primary packaging process, whereas syringes and cartridges exit the filling machine in their tub.

Processing vials in bulk (in a step-by-step process flow)

Bulk vials follow a different path. The vials are manually removed from their overwrapping and loaded onto the rotating table of the RA-V4 Rotary Washing Machine where pincers automatically pick up each vial and reposition it for optimal spray **cleaning and drying** during its passage through washing and drying stations. These stations are equipped with needles which are lifted inside the vials where water for injection (WFI) and compressed air are sprayed. After washing and drying, vials are automatically discharged onto the conveyor belt between Washer and Depyrogenation Tunnel. The Rotary Washing Machine integrated control system, which includes a Programmable Logic Controller (PLC) and a Human-Machine Interface (HMI), automatically controls all the functional parameters of the machine, according to various vial sizes and types. Parameter data is stored in different recipes, which are password protected and accessible only by supervisor and authorized personnel. The RA-V4 has a footprint of 1,500 mm x 1,476 mm and it is designed to process up to 7,200 vials per hour. Parts coming in contact with the interior of the vials and process fluids are made of AISI 316L stainless steel, while other parts are made of AISI 304 stainless steel. RA-V4 is compliant with current Good Manufacturing Practices (cGMP), Good Automated Manufacturing Practice (GAMP) and title 21 of the Code of Federal Regulations Part 11 (21CFR Part11) requirements.

Once the vials are washed, the VP300 Vial Pusher (under Laminar Air Flow [LAF]) pushes the vials into the ST0-CCS Depyrogenation Tunnel designed with a footprint of 1,670 mm long, 1,260 mm wide and 2,400 mm high.

The ST0-CCS is composed of three chambers: the **inlet chamber**, the **hot chamber** and the **cooling**

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chamber. The inlet chamber with its laminar flow unit dries and preheats glassware, protecting the vials from the hot air back flow coming from the hot chamber. The hot chamber subjects the glassware to the thermal cycle for depyrogenation. The treatment undertakes glassware at a temperature that ranges from 250 up to 340 °C to achieve the required 6 Log Reduction result. **Log reduction** is a mathematical term that is used to express the relative number of living microbes that are eliminated by decontamination. The duration of this process changes according to the production speed needs. The machine follows validated recipes that have been set to unique time and temperature parameters according to the vial size.

The cooling chamber removes heat from the glassware in a controlled cool-down to reduce thermal shock to the vials. An insulated airtight door at the tunnel exit, equipped with high temperature resistant inflatable gaskets, protects the filling isolator during the cooling chamber sterilization. The cooling chamber is sterilized by High Efficiency Particulate Air (HEPA) filtered hot air at a temperature of 160°C. ST0-CCS conveyor belt width is 300 mm and depyrogenation is performed by 242 m³/h inlet air. Once glassware cooling achieves the suitable temperature, the vials are discharged onto a LBT to reach the RT600 Rotating Table.

The vials are loaded onto a conveyor belt that enters the filling isolator. A robotic arm grabs a line of vials at a time and inserts them in an empty nest. Once the nest is filled, the robot places the nest on the filling station of Colanar Filling and Stoppering machine where they are filled and stoppered as required. A second robot removes the filled and stoppered vials and place them on a conveyor that exits the filling isolator through a shutter gate. The vials are either expelled into the IMA freeze drier when the product requires lyophilization or directly toward the Genesis Capping Machine for the capping process.

An isolator-based line for sterile packaging

In addition to the machines, Steriline delivered to BSM the Isolators (ISOs) required for the Colanar Filling Machine and the ORABS for the capping machine. Steriline ISOs are designed to produce sterile products, either toxic or non-toxic, maintaining uncompromised, continuous separation of its interior space from the external environment. ISO 5 environment is achieved by HEPA filtered, unidirectional air that vertically flows over the process area. Pressure difference between the interior and the exterior is maintained by the exhaust fan. The exhaust air is HEPA filtered by “bag-in bag-out” (BIBO) filters.



Fig. 3 – Steriline isolators guarantee the sterile environment for a safety packaging

The surfaces of Steriline ISO that come in contact with the product are made of AISI316L stainless steel, and the parts not in contact with the product and sanitizing solution are made of AISI304L stainless steel.

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Cleaning solution piping with tri-clamp fittings are made of AISI316L stainless steel. ISOs are also equipped with gloves for interventions by the technicians and handling of Environmental Monitoring (EM) components. Continuous EM of viable and non-viable particles is included. The integrated control system of ISOs is composed of PLC and touch screen operation panel for HMI.

Integrating solutions of five suppliers

As BSM required the solution to process different formats of glassware, five suppliers collaborated to develop the line to process up to 3,000 units/hour from 2R to 100R vials in RTU tubs, from 0.5 mL to 5 mL syringes and 3 mL cartridges. In addition, the solution can manage vials in bulk from 2R to 100 mL-VI53 with a production capacity that ranges between 3,000 units/hour to 900 units/hour.

The solution can run one production cycle at a time. However, the freeze dryer, which may need up to several days to freeze dry the products, is designed to work independently leaving the rest of the line to manage a production batch that does not require lyophilization, bypassing the freeze dryer.

This line increased the company's **production capacity** allowing BSM to service clients further in their clinical studies and attract new ones for flexibility and state-of-the-art equipment.

A peculiarity of the project concerns in the involvement of five different suppliers that collaborated with the aim of a complete line. After the submission of the orders to Claranor, Colanar, Genesis, and IMA, Steriline, as the main supplier, played a primary coordinating role for the integration of all the equipment and offering a cost-effective and fully automated solution which met all BSM's requirements and desires for a new line. Moreover, the timeline offered by Steriline was also acceptable to BSM.

*"We selected Steriline – said **Shawn Kinney, CEO** at BSM – to work with several other selected equipment manufacturers to fully integrate and create a state-of-the-art, isolator-based sterile filling line because they were a reputable company with a solid track record for providing a high-quality product. This filling line incorporates innovative technologies never used before in small volume aseptic fillers. The line sets a new standard of sterility assurance and technology in aseptic manufacturing, and it has been operational since November 2022".*

Since September 2020, when the project launched at the Steriline factories, the need to **share information** among the involved players has been significant. Steriline, supplying the largest number of machines to the solution, coordinated the alignment activities between the teams of the five suppliers and BSM. **Eleonora Rizzi, Project Manager at Steriline**, says *"Bi-weekly meetings have become a fixed appointment for more than a year, requiring constant commitment also from the management point of view to update all players. BSM shared an agenda of topics in preparation for each meeting and, depending on the issues, we involved our technicians to ensure a quality sharing of information with the other teams."* In addition, there was also a direct one-to-one relationship between suppliers to address detailed issues for the integration of specific machines. Steriline made a series of meetings with both Colanar and Genesis to solve technical incongruences, from dimensions to speed and capacity, and to integrate the Supervisory Control And Data Acquisition (SCADA) systems of the machines.

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Moreover, during the project development, suppliers were faced with supply-chain issues of electrical and electronic components due to global shortages during the COVID-19 pandemic. The delivery of HMI screens was delayed, challenging the project on-time completion.

In alignment with BSM, Steriline split Factory Acceptance Tests (FAT) of the machines handling the bulk from the machines handling RTU tubs. In August 2021, RA-V4, VP300 and ST0-CCS were tested remotely since travel between the US and EU was restricted. Steriline adopted a series of cameras to film and livestream the procedures for BSM to oversee from their facility.

In November 2021, when travel was again possible, the RTU section of the line in addition to their respective Isolators (RT600, LBT, SDB, RTDS2, and ADE) were tested at Steriline in the presence of BSM's team, and in February 2022 the remainder of the line was delivered to BSM. In the following months, Steriline has installed and started up its machines and finally performed the Site Acceptance Test (SAT).

Ron Trefzger, Associate Director of Engineering at BSM, recounts the complexity yet efficiency of this project: *"Integrating equipment from five companies into one line was a huge project. We asked for a completely unique design and process flow to be able to process multiple container types and sizes in order for the line to fit our needs. Steriline has been instrumental in designing a solution to meet our needs and incorporating equipment from other suppliers to create a flexible, high-quality, and innovative line. Communication was constant, and progress was steady."*

Federico Fumagalli, Chief Commercial Officer at Steriline, confirms *"The relationship between us and our customers is visceral. Listening to them is crucial to understand their needs, develop personalized solutions and teach them how they can maximize the value of our solution. Customer satisfaction is a lever for further ambitious collaborations and the developing of new technologies and products at the state-of-the-art."*

After the installation of the solution, Steriline has also planned a training course to BSM on the new isolator system.

For more information about **Berkshire Sterile Manufacturing**: www.berkshiresterilemanufacturing.com

For more information about **Steriline**: www.steriline.it or visit the Company profile on **LinkedIn**.