# Value and practical implementation of a modular aseptic filling platform for use with complex and personalized parenteral drug products in powder, liquid, suspension or combination form

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## Overview

The number of complex and personalized parenteral drug products that are in clinical development or approved for human use continues to expand rapidly. This growth has subsequently increased demand for specialized aseptic fill finish equipment and related services that can provide the necessary versatility to load such drug products into vials or other primary containers. To complement its range of CDMO services available to customers with complex or personalized parenteral drug products, Evonik has recently installed and qualified a VarioSys® Aseptic Fill Line at its parenteral drug product manufacturing facility in Birmingham in the U.S. State of Alabama. To reduce project time and cost while simplifying production complexity, the VarioSys® line built and integrated by Bausch + Stroebel features a 3-section modular design that enables efficient exchange of equipment configurations to fit a variety of filling process requirements for powders, liquids and suspensions, or their associated combinations.

## Introduction

An increasing number of drug products in clinical development and approved for human use are highly specialized in formulation, requiring advanced drug delivery technologies to deliver small molecules, peptides, proteins, and nucleic acids for new treatment modalities across a wide range of therapy areas (1). Such drug products may be designed for systemic delivery, localized delivery to sites such as the eye, joints, brain, organs, tumors and the spine, as well as the targeting of specific genes or disease sites.

Complex parenterals can face many significant manufacturing challenges including formulation stability affecting the final dosage form, various intricacies relating to high-mix / low-volume cGMP manufacturing capabilities, and the method of sterility assurance. For example, terminal sterilization methods such as gamma irradiation are commonly used for many drug products due to its effectiveness and reliability. However, for many complex parenterals, terminal sterilization can often result in product degradation and loss of effectiveness (2). This incompatibility can necessitate the implementation of specialized solutions for the aseptic manufacturing and filling of such drug products.

In parallel, demand continues to increase for the development of drug products that are either individualized to specific patients or designed to treat various rare or genetic diseases. New modalities that fall under ‘personalized medicine’ umbrella will, by definition, have smaller batch sizes.

Traditional aseptic filling lines lack the necessary versatility to handle such highly specialized drug products. It is also cost-prohibitive to develop customized filling lines that are equipped to handle each specific type of specialized or personalized drug product given the significant process variabilities and low batch volume requirements. Furthermore, such novel or highly customized filling lines would require between two and three years on average to proceed from initial design to full qualification and readiness for cGMP manufacturing, potentially obstructing the path to market for promising drug product candidates (3).

To address this unmet market need, pharmaceutical equipment manufacturers and CDMOs for complex parenterals such as Evonik have sought to develop a new generation of aseptic filling lines that provide sufficient modularity to support cost-effective manufacturing of multiple types of drugs. One such system is described herein, the Bausch + Stroebel VarioSys® Fill Line.

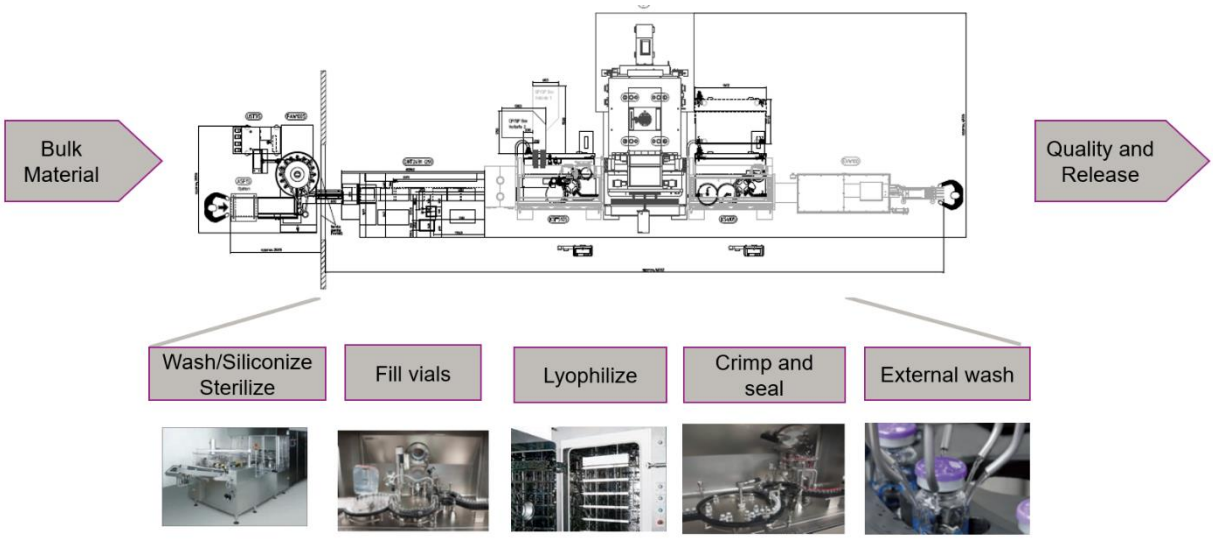



*Figure 1 Schematic of VarioSys® Aseptic Fill Line*

Evonik installed and qualified this VarioSys® Aseptic Fill Line from Bausch + Stroebel (4) at its parenteral drug product manufacturing facility located at Birmingham in the U.S. State of Alabama. (Figures 1 and 2). Evonik's VarioSys® line features efficient interchanging of equipment to fit each filling process step for powder, liquid or suspension combinations making the fill line ideal for low volume, high mix manufacturing. This line is fully capable of aseptic processing which is demonstrated through Evonik's established media fill program. It features integrated lyophilization capabilities to realize the improved stability of drug products that require this processing step. With a capacity fill per shift up to 18,000 vials in powder form and 24,000 vials in liquid, suspension of lyophilized form, the Variosys® Fill Line can support the clinical or commercial scale requirements of a range of complex drug products and vaccines all within a compact 6.5 $m^2$ of isolator space.

*Figure 2: VarioSys® Aseptic Fill Line*

## Technical features VarioSys® Fill Line

### *Flexibility*

The flexible design of the VarioSys® Fill Line features SKAN PSI-L (Pharmaceutical Safety Isolator L-Flange) (5) and SARA (Safe and Rapid Airlock) isolator technology. The advanced L-flange technology allows the user to adapt the line most closely to the specifications of each customer. Isolator internals are on movable trolleys that can be largely individualized with equipment that best fits the desired process (6). The equipment is installed directly onto the modular trolley, and integrated with the isolator, by simply rolling the trolley in place and inflating the gaskets. This process, which can be completed in approximately 30 minutes, allows fill line equipment to be rapidly reconfigured based on the process requirements of each program. As such, the line can be easily adapted for different products and container types such as ready-to-fill syringes thereby limiting equipment downtime. Furthermore, filling equipment can be completely removed from the clean room for maintenance, while the line continues to run with a different trolley module installed.

*Figure 3: Bausch + Stroebel Powder Filler*

### *Modality*

The VarioSys® Fill Line has the capability to aseptically fill powder, liquid/suspension and even both during production, with the added option of lyophilization. Rather than having separate filling systems operating in tandem within a facility, both powder and liquid filling can occur in the same Grade A isolator modular chamber. The integrated dual filler is fed by a ChargePoint (7) valve for powders and a peristaltic pump for liquids and suspensions.

The VarioSys® high-precision powder and liquid filler minimizes product loss, and automatically adjusts while running to optimize filling precision. The system is also optimized to have almost no residual powder after the batch. A top-off feature eliminates underfilled vials, while a weight check feature allows for 100% weight check verification to maximize quality control. Its compact design also allows product tanks or vessels to be placed close to the machine to minimize product loss in transfer tubing. Adding to the flexibility of the fill line, an optional nitrogen overlay can take place in the filling isolator chamber to allow handling of oxygen-reactive or humidity-sensitive products.

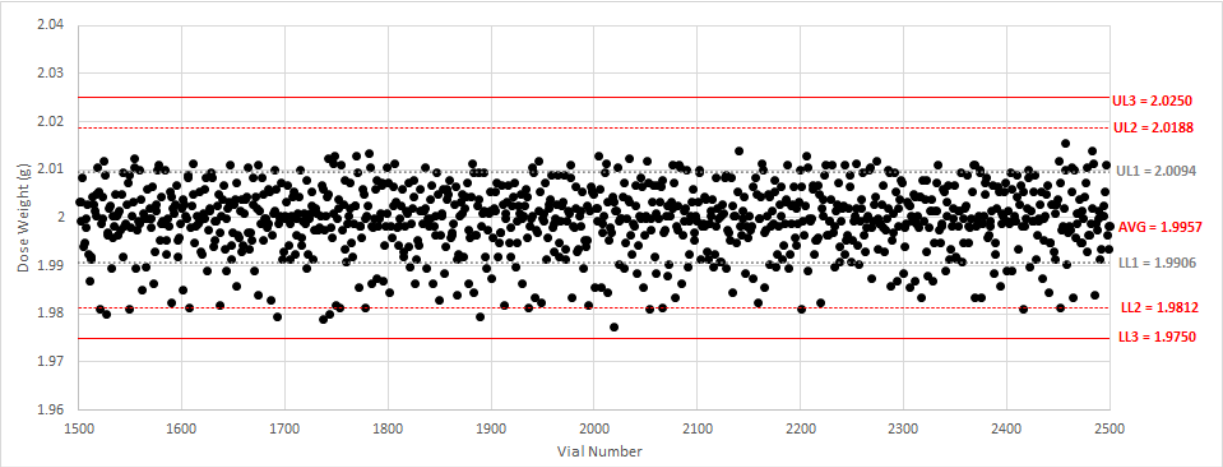
The ChargePoint AseptiSafe® Bio split butterfly valve allows for aseptic powder transfer into the Bausch + Stoebel powder filler (Figure 3). The valve's VHP (Vaporized Hydrogen Peroxide) capability offers increased sterility without the limitation of storing the bulk API inside the isolator. Multiple API vessels and containers can be used during a single batch and can be switched out without having to pause filling activities.

From the ChargePoint valve, product is fed volumetrically into the dosing container using a vibration-controlled feed pipe and then gravimetrically doses vials. Product volume in the dosing cup is kept at an optimal fill height using automatic level control to prevent powder from packing down either too much

or too little.  Interchangeable dosing size parts allow the filler to be adapted to fit almost any type of powder product in less than 15 minutes. The combination volumetric and gravimetric filler also enables consistent product control and precise dosing down to ±0.2% for many formulations  (Figure 4).

*Figure 4: Dosing accuracy*

**A:**

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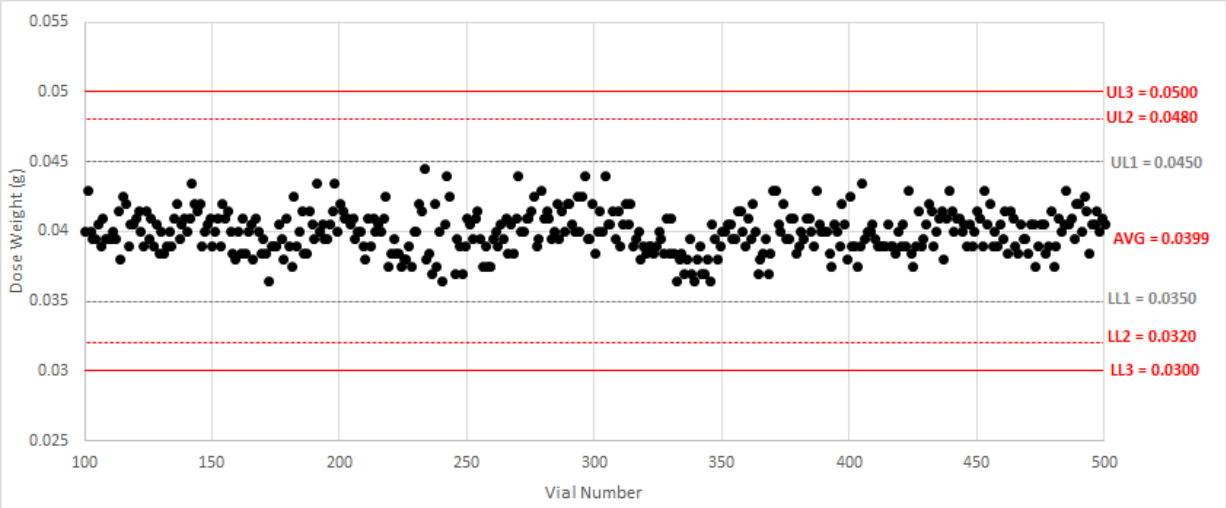


Figure 4: Dose weight distribution of liquid or powder filled vials. A: Dose weight distribution of 1000 vials dosed using the Bausch + Stroebel liquid filler with a target weight of 2.000 grams. The average weight of this distribution is 1.9957 grams, with none of the vials exceeding the minimum or maximum net weight limits. B: Dose weight distribution of 400 vials dosed using the Bausch + Stroebel powder filler with a target weight of 0.0400 grams. The average weight of this distribution is 0.0399 grams, with none of the vials exceeding the minimum or maximum net weight limits. UL1: maximum net weight limit for no adjustment, UL2: maximum warning limit, UL3: maximum net weight, LL1: minimum net weight limit for no adjustment, LL2: minimum warning limit, LL3: minimum net weight.

An integrated peristaltic pump precisely feeds viscous liquids up to 35 cP within a filling range between 0.1 to 100.0 mL. The design minimizes shear to protect shear-sensitive products. Different ~~pumps~~ filling methods may be used when installed on a new L-flange to handle products with special requirements without buying the entire new isolator/filling system.

Stability and shelf life of complex parenterals can be a challenge. One method to increase the stability of certain drug products is lyophilization. This process of freezing and subliming liquid, leaving a dry powder behind, requires precise control and containment to preserve product sterility. VarioSys® includes the GEA LYOVAC™ Lyophilizer (8), which utilizes ALUS™ (Automated Loading and Unloading System) technology. ALUS seamlessly loads vials into the lyophilizer chamber as they come off the filler, with minimal operator intervention, then unloads them automatically after the freeze dry cycle. If products do not require a lyophilization step, vials will bypass this unit and enter the capper/crimper system in the next module. This streamlined system provides a benefit of lowering the risk of vial transport loss between the traditional lyophilization wall units and the one integrated in the VarioSys®.

The capper/crimper installed on the VarioSys® Fill Line is designed to match the pace of the filler to keep the processing line running smoothly (Figure 5). The capper/crimper maximizes efficiency by automatically performing a full check from stopper insertion through to the final crimped seal. When the vials enter the crimper, a stopper check is performed to verify the stopper is properly seated so the seal can be placed appropriately. The sterile unit is sealed and checked by several sensors before the vial moves on to the final external vial washing station. Vial ejects are automatically segregated.

*Figure 5: Capping and Crimping Isolator Chamber*

The VarioSys® Fill Line is equipped with a PennTech (9) External Vial Washer post capping that further ensures operator and customer safety when handling high potent APIs (Figure 6). The negative pressure enclosure rinses vials with WFI (Water-for-Injection) while also providing the option of adding a detergent to clean potential contaminants from the outside of the vials. Following vial washing, vials go through a blow-dry station prior to automatically transferring to the off-loading table. The whole process is completed in a controlled and contained system until the final off-loading table, enabling the VarioSys® to operate in a fully integrated manner with no delays, even for highly potent products.

*Figure 6: PennTech External Vial Washer*

### *Sterility*

The SKAN isolators create a fully integrated, sterile environment. A successful VHP cycle must successfully run for the isolators to move into Production Mode. Integrated active air samplers are installed in each chamber with two in the filling chamber and the filling system automatically stops all filling operations if acceptable levels are exceeded. The SARA airlock, which can be completely sealed off from the other isolator chambers, allows components to be added to the fill line in a sterile manner without breaching the main chambers – a critical function for longer production activities. Once components are introduced into the SARA, a single VHP cycle can be performed, after which the SARA can be opened to the other isolator chambers and materials can be passed through. The ability to utilize the SARA airlock in this manner adds a dimension of flexibility while maintaining aseptic environment that is not easily achieved in traditional fill lines.

The Bausch + Stroebel Depyrogenation Tunnel continuously supplies sterile vials throughout the entire filling process, all while limiting operator intervention. Vials are fed, washed, and depyrogenated in an inline process that transports sterile vials into the isolator in under two hours. The Bausch + Stroebel Depyrogenation Tunnel also allows an unlimited number of vials to enter, but also allows the operator to pause filling activities, if the operation is not running 24-hour shifts, and resume on the next day. This mode allows for maximum efficiency and minimal start-up for a multi-day batch.

### *Scalability*

All the topics above add to the scalability of the VarioSys® system so that it has the versatility to handle a wide variety of complex and sensitive parenterals while optimizing the time to market. With an ever-adapting industry that increasingly utilizes smaller batch sizes as opposed to full-time production, the VarioSys® offers the option of a flexible line that can quickly fit to each product (Table 1) reduces cost by minimizing product loss and provides an accessible, low cost solution for modifying a process without a complete rebuild or retrofit. The fill line is currently capable of processing vials as small as 2mL and up to 50 mL, but new size parts can be designed to accommodate different vial sizes or shapes for future projects.

## Table 1: Current VarioSys® Capabilities

| **Bausch + Stroebel VarioSys®** | | |
|---|---|---|
| Fill Type (single head) | Powder | Liquid / Suspension / Lyophilization |
| Vial Size | 5 – 100 mL | 2 – 100 mL |
| Batch Size | up to 18,000 vials/shift | up to 24,000 vial/shift |
| Lyophilizer Area | | 4.7 $m^2$ (50.6 $ft^2$) |
| Lyophilizer Batch Size (up to 50ml vial) | | 22,100 @ 2 mL (15 mm)<br>3,700 @ 30 mL (37 mm) |
| Fill Volume | 35 mg to > 1 g | 0.1 to 100 mL |
| Line Speed | max. 3600 vials / hr<br>(max 60 vials / min) | |
| Capability | General Compound Handling<br>High Potent<br>Controlled Substance / Scheduled Compounds | |

## Case Studies

One of the first commercial clients on Evonik's VarioSys® Fill Line is utilizing the line's powder filling capabilities along with a low oxygen, nitrogen rich environment which can reach low oxygen concentration limit of 13.5% vol. Nitrogen flushing in the filling chamber is necessary for a variety of reasons, but in this case it keeps the oxygen level below the product's level of combustibility (LOC) while also lowering the humidity within the chamber to protect the moisture sensitive product. A product lift elevates and inverts the client's product vessel as it is connected to the ChargePoint valve or is adaptable to a variety of other product containers. Further quality assurance is provided by continuous sensor trends for each isolator chamber across critical parameters of temperature, humidity, oxygen concentration and other environmental conditions throughout the production batch.

The versatility of the VarioSys® Fill Line can be further illustrated with another Evonik client requiring a dual fill and lyophilization process for a liposome-based product formulation. The configuration for this client involves an initial liquid fill, in which vials are filled with a liposome solution, a subsequent lyophilization cycle, and then a second fill with an API overlay solution, before the vials proceed to the capping, crimping and final washing. For this filling production, the final chamber may modified to include liquid filling equipment, in addition to the capping and crimping machine. While a traditional stationary line would need to be rebuilt for such applications, the VarioSys® can be readily adapted to reduce cost and the time to production by only modifying a smaller module rather than an entire fill line.

## Conclusion

Complex pharmaceutical formulations will continue to evolve, demanding newer adaptable equipment to fit these unique pharmaceuticals. Versatile filling lines need to be capable of handling sensitive parenterals that also require unique compound handling. Pharmaceutical innovators need to have both the advantage of moving quickly to patients, but also having the highest quality standards for the final product. Evonik has recognized these emerging needs with its implementation of this VarioSys® to further complement its broad portfolio of capabilities for complex parenterals, including parenteral excipients, and formulation, process development and cGMP drug product manufacturing.

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