Cytiva aseptic filling workcells and Annex 1

Designed to be used for manufacture of drug products in accordance with EU GMP Annex 1 guidelines

The SA25 Aseptic Filling Workcell is the first standardized, robotic filling solution fully integrated into a closed, gloveless isolator to be used in commercial fills for drug products approved by the FDA, Health Canada, PIC/S, and NMPA. Here, we answer common questions regarding how our aseptic filling workcells are designed to be used by drug product manufacturers for aseptic filling in accordance with the most recent revision of the EU GMP Annex 1: Manufacture of Sterile Medicinal Products for aseptic processing regulatory guidelines.

Frequently asked questions

How do closed, gloveless isolators compare to other barrier technologies used for aseptic fill finish?

Barrier technologies are intended to provide product protection and quality assurance by increasing the separation of the operator from critical activities and reducing the risk of microbial contamination. Restricted access barrier systems (RABS) and isolators (both closed and open) are considered barrier technologies. RABS typically achieve a basic level of such separation via curtains, panels, and doors. Isolators take the separation further via stainless steel cabinets. However, in most isolators, operators still have access to the aseptic process by means of gloves. Although glove technology has improved, allowing operator interventions through gloves is an engineering control that increases the risk to both product and patient. The SA25 eliminates operator intervention. It is a closed, gloveless isolator that is fully automated, with all material handling and filling performed robotically.

The SA25 removes key hazard pathways by means of:

- Removal of both direct and indirect product contact parts, e.g., stopper bowls, rails, and conveyors used in conventional filling systems
- Reducing the risk of particle introduction from crimp capping by simplifying the capping process to a single step using press-fit polymer caps that secure the stopper to the vial
- Elimination of container damage and particle generation due to container-to-container contact, by handling the primary containers and closures in nested format (the SA25 uses nested containers, thereby keeping all containers separate)
- Elimination of risks related to aseptic assembly within the Grade environment by using a sterile flowpath that is set up prior to isolator decontamination and opened robotically

Is the Cytiva SA25 Aseptic Filling Workcell suitable for broad commercial manufacturing?

The SA25 technology is designed to support small batch production in accordance with Good Manufacturing Practices (GMP) and has been used at a number of manufacturing sites, including WuXi Biologics and Emergent BioSolutions. As such, the SA25 is suitable for commercial manufacturing of drug products requiring small batch sizes such as personalized medicine. It supports all phases of clinical production and scales out to move from clinical to commercial production. The intended batch size can be as low as 100 units up to 20 000 units and beyond. The SA25 also reduces the tech transfer operating risk and streamlines the qualification process. Multiple customers have already received regulatory approvals to manufacture commercial drug products using the SA25.

How is the DSI (Decontamination and Staging Isolator) classified?

The DSI is a material airlock/pass-through chamber and is designed to contain all the features for a material airlock that are described in Annex 1 (subsections 4.12.ii, 4.13). The design of the workcell allows for complete processing through final closure of the filled units within the isolator and does so in a way that minimizes exposure and provides nest-by-nest segregation throughout the batch.

How are contamination risks handled in the SA25?

Material transfer into and out of an isolator is potentially the greatest remaining contamination risk with barrier systems. As a closed isolator, the SA25 further reduces this risk by eliminating the “mouseholes” commonly used to move components into and out of the workcell during production. The DSI chamber is used to load and stage tubs of ready-to-use (RTU) components. Only pre-sterilized components in sealed tubs enter the DSI, manually loaded

by the operator, after which the DSI remains closed to the cleanroom background. The outer surfaces of the tubs are decontaminated with vapor hydrogen peroxide before sequentially entering the filling isolator. The filled and sealed containers subsequently return to the DSI. Only after processing all the tubs originally loaded is the DSI opened to remove the finished product, while the inner door to the filling isolator remains closed, protecting the critical zone. Multiple cycles of the DSI can be run to achieve the desired batch size. The DSI design also allows for post-fill surface decontamination of filled, closed containers, which is an important consideration when filling viral vector products.

A proprietary needle design removes the risk of incorrect operator aseptic technique potentially compromising the sterility of the fill needle and flowpath. The flowpath is pre-sterilized by gamma irradiation and installed prior to decontamination by the operator. The needle assembly has a security seal that indicates that the sheath has not been opened post-sterilization. The needle is robotically opened by the fill robot, breaking the seal, after decontamination. An impermeable elastomeric sheath protects the silicone tubing from exposure to hydrogen peroxide.

All material handling is performed robotically after the decontamination phase, including transfer of filled containers to the stoppering chamber for closure. Human intervention is not possible, and all interaction is through the human-machine interface (HMI).

What is the difference between vertical and horizontal airflow, and does it impact product protection?

Airflow in aseptic filling isolators is based on their predecessors, either cleanrooms with ceiling-installed HEPA filtration or grade A laminar airflow hoods (LAF). In reality, airflow is not laminar but unidirectional, defined in Annex 1 as, "an airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed, to reproducibly sweep particles away from the critical processing or testing area." The purpose of the unidirectional airflow is to remove contamination that may be deposited into the airflow and to limit the potential for contamination of critical surfaces either by gravity or turbulence. This can be achieved by using either vertical or horizontal airflow at an airflow velocity that is adequate for the process. It can also be achieved through appropriately applying engineering controls, for example, through design mitigation. Eliminating the operator and reducing particle generation is the primary risk mitigation, and applying airflow is an additional protective control that can be layered on top of design mitigation. Both horizontal and vertical airflow are acceptable, providing that airflow is demonstrated as traveling at a sufficient speed to support single direction, uniform flow characteristics. Again, unidirectional airflow is only one layer of product protection and should be reviewed as part of a holistic contamination control strategy.

How does the SA25 workcell meet the "first air" principle as required within Annex 1?

Both horizontal and vertical airflow systems are used throughout the biopharmaceutical industry, specifically in the drug fill and production space. The definition of "first air" per Annex 1 refers to "filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone." It would not be possible to dispense product into an open container without interrupting the airflow over the open containers with the fill needle at a minimum. In the case of most standard filling systems, aseptically assembled parts, tubing, and machine parts are in constant motion over the top of the open containers. Throughout Annex 1, it can be seen that "first air" is mentioned specifically in relation to personnel movement and glove manipulations, which are widely accepted as the primary contamination hazard pathway, between the air source and open product (4.20.i.b, 7.18). The greatest protective element for the aseptic process is the elimination of the operator and the maintenance of an integral barrier. Airflow is an additional protective control that is layered on top of design mitigation. The SA25 is designed to comply with "first air" principles by providing an integral, high-quality environment with simplified processing of pre-sterilized components and complete elimination of the operator.

How does the design of the SA25 workcell help to ensure appropriate monitoring of filling activities in line with Annex 1 guidelines?

Annex 1 does not differentiate between the monitoring requirements for each of the various barrier technologies, but it does specify both "frequent" and "continuous" monitoring of Grade A environments. The SA25 workcell was designed to control the risk of contamination by applying Quality Risk Management (QRM) principles. The gloveless design of the SA25 workcell eliminates the operator and, with ready-to-use (RTU) components, eliminates any onsite processing of the primary container/closures such as washing, depyrogenation, and handling of stopper bowls, tracks, and other means of component transport. Thorough environmental monitoring risk assessments highlight the reduced risk associated with the design of the SA25 and the rationale for reduced monitoring requirements. Appropriate pre-production monitoring and trending is performed to demonstrate the control of the pre-production environment and support the in-process monitoring.

There are several key features that help the SA25 maintain an ISO 5/Grade A filling environment:

- Positive pressure maintained against the cleanroom. The DSI is a material transfer chamber, operating at a lower

differential pressure to help ensure air from the DSI is not migrating into the filling isolator (FI).

- Decontamination with vapor phase hydrogen peroxide (VPHP), validated to achieve a 6-log10 kill of viable resistant spores deposited on biological indicators (BI)
- No glove ports for human intervention
- A single product-contact assembly—the flowpath—which is robotically opened with no aseptic setup

The VPHP decontamination cycle, coupled with the fact that the isolator is truly closed throughout processing, renders insignificant any risk of introducing bioburden post-decontamination. Even so, the systems are designed to monitor the environment utilizing continuous non-viable air sampling, product contact surface sampling, and active viable air sampling performed at user-defined frequencies throughout production. The active viable air sampling is typically a $1m^3$ sample per DSI load. This approach provides a low-risk alternative to conventional, passive monitoring such as traditional settle plates. More frequent monitoring may be performed as determined by the manufacturer's quality system.

How is container closure performed inside the SA25 and how is product protection maintained?

The SA25 design eliminates the need for indirect contact parts (stopper bowl) by using an integrated stopper and plastic cap design. Stoppering and closure of vials are performed in a single step inside the stoppering chamber. The nested polymer caps/stopper are pressed onto the vials and then transferred back to the DSI, fully sealed. There is no aseptic transfer of stoppered-but-not-capped vials or operator intervention required. The stoppering chamber can also be used for inert overlay and the vacuum stoppering of syringes/cartridges.

The regulatory requirement for active Grade A-supplied air is related to stoppered-but-not-capped units exiting the Grade A environment prior to the crimp capping operation, as performed on most filling systems. The stoppering chamber can be seen as similar to that of a lyophilizer, where the units are open and there is no active Grade A airflow or monitoring. Annex 1 allows for alternative process methods provided there is no increased risk to the product, which has effectively been demonstrated during qualification of the SA25.

How is non-viable particulate contamination controlled?

The SA25 was designed to provide an environment with low particulate contamination. This is achieved primarily through the design of a process that handles pre-sterilized nested parts. Containers and closures are kept in their nested format for the entirety of the aseptic process, reducing mechanical complexity and reducing material handling to pick and place. Glass-to-glass contact and related damage and particulate generation are eliminated. The use of pre-sterilized, integrated polymer cap and stopper removes the particle generation associated with aluminum crimp capping.

Tub peeling takes place downstream of filling activities in a horizontal unidirectional airflow, in front of one of the exhaust HEPA filters. This facilitates the removal of smaller particles that may be generated. Airflow visualization studies support that airflow remains unidirectional and does not contaminate the filling zone. RTU component manufacturers have designed their tub covers to be peeled, with an inner liner placed over the open vials to protect them during the peeling process. The SA25 uses machine vision to verify the presence of the inner liner before it is removed.

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