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The Logistics of Filling and Freeze Drying using Multiple Isolators.

The use of isolator technology to fill and lyophilize pharmaceuticals presents many logistical challenges. Aventis Pasteur has developed procedures to fill, partially stopper, freeze-dry and cap its products in the Pilot Plant using three isolators (Transfer, Filling, and Lyophilizer). The equipment was designed to fit into an existing space, which also presented some significant challenges. The equipment has been installed and validated for the aseptic filling and freeze-drying processes for clinical supplies.

Justification

The traditional method of preparing the investigational supplies was filling on the licensed filling line in Manufacturing, or hand filling in the pilot plant. Recent FDA initiatives, requiring a notification and associated validation requirements for filling of non-licensed products on a licensed filling line has made this quite cumbersome and at times not possible, as with live vaccines. Also the scheduling of these non-licensed products to be filled on the manufacturing line prevented the flexibility needed to meet the clinical requirements.

Another consideration was the scale of the commercial filling line. Quite often the volume of the clinical vaccine approached the hold-up volume of the commercial filling line, thus product losses would be unacceptable.

While hand-filling operations were easy to perform and schedule with virtually no losses due to scale, the reduced sterility assurance made this option less attractive. Contract filling manufacturers was another option we explored, however the number of contract fillers was limited and very few would fill live material.

Therefore, the decision was made to invest in a pilot plant filling and freeze-drying facility. The only question we faced was which technology to choose? The traditional clean room or barrier technology? We did a positive/negative analysis on both the clean room and barrier technology and the positives of barrier far outweighed the clean room. Some of the positives being:

- High degree of sterility assurance
- The entire filling environment can be sterilized
- Cost equivalent to traditional filling lines
- Only A class “C” surrounding environment required
- Containment and decontamination of the isolator

Equipment and Facility Design

As with many companies, space limitations are a common drawback in designing and implementing processes. Aventis Pasteur is no different. When the Development Department was charged with designing, purchasing, installing and validating a filling and freeze-drying facility, approximately 400 sq. ft of floor space was available to perform these operations. The facility would be used for filling and freeze drying phase 1 & 2 clinical supplies up to 10,000 doses, live bacterial or viral master seeds, and test reagents and standards.

We contacted the equipment suppliers for the desired scale for the isolators, filling equipment, lyophilizer, vapor phase hydrogen peroxide (VHP) generator and room design and construction. The specifications and facility design were developed from our internal user requirements, current FDA requirements and with discussions with the equipment suppliers.

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We prepared scale drawings of the equipment and personnel, which we used to determine the basic layout of the equipment. After several design attempts, it was determined that three isolators would be required to perform the desired operations within the 400 sq. ft. room. These included a filling isolator, a lyophilizer isolator and a transfer isolator. We used plywood mock-ups in the design phase enabling us to specify the correct size and function of the isolator to meet our needs.

The transfer isolator (figure 1) is a mobile isolator with turbulent HEPA filtered inlet and ULPA filtered exhaust airflow, and it maintains a +ΔP to the surrounding environment. All materials of construction are of sanitary design and are VHP compatible. It is fitted with a 350mm flexible rapid transfer port (RTP) and a Boyer door for the loading of equipment. It has 5 glove ports and environmental monitoring ports for both viable and non-viable particulate monitoring.

Figure 1: Carlilse Barrier Transfer Isolator

The main function of the transfer isolator is to:

- Sterilize the exterior surface of the filling components
- Supply filling components to the filling isolator
- Transfer partially stoppered vials to the lyophilizer isolator
- Transfer the stoppered lyophilized vials to the filling isolator for capping and crimping

The Lyophilizer isolator (figure 2) is a stationary isolator with turbulent HEPA filtered inlet and ULPA filtered exhaust airflow, and it maintains a +ΔP to the surrounding environment. All materials of construction are of sanitary design and are VHP compatible. It is fitted with a 350mm docking (RTP). It has 4 glove ports and environmental monitoring ports for both viable and non-viable particulate monitoring.

The main function of the lyophilizer isolator is to:

- Accept the partially stoppered vials from the filling isolator
- Provide a sanitary environment to load and unload the freeze-dryer
- Transfer the stoppered lyophilized vials to the transfer isolator

The filling isolator (figure 3) is a stationary isolator with unidirectional recirculated HEPA filtered airflow with turbulent HEPA filtered inlet and ULPA filtered exhaust airflow, and it maintains a +ΔP to the surrounding environment. All materials of construction are of sanitary design and are VHP compatible. The filling isolator is temperature controlled at 70^{O}F. It is fitted with a 350mm entrance and exit RTPs for the loading of equipment and the transfer of partially stoppered and freeze-dried vials. It has 9 glove ports and environmental monitoring ports for both viable and non-viable particulate monitoring. It

Figure 2: Carlilse Barrier Lyophilizer Isolator

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houses the filling equipment. It also has one 270mm RTP for docking of the autoclavable filling component canisters and one 105mm RTP for docking the filling needle/tubing canister.

The main function of the filling isolator is to:

- Accept the filling components and the product feed
- House the filling, stoppering, capping and crimping operations
- Transfer partially stoppered vials to the transfer isolator
- Accept the stoppered lyophilized vials from the transfer isolator for capping and crimping

Figure 3a: Carlilse Barrier Filling Isolator (Front view)

Figure 3b: Carlilse Barrier Filling Isolator (Rear view)

The filling machine (figure 4) is single-needle filler, which is fed by a peristaltic pump. The filling line is on an elevated platform to minimize any air turbulence at the filling area. All materials of construction are of sanitary design and are VHP compatible. All penetrations are covered with a bellows. The mechanical adjustments are all tool-free. It can fill 2-50ml vials in both 13mm and 20mm stoppers and caps. The unit will fill at approximately 30-35 vials/minute, for the 3ml vial size. The unit is operated by an Allen-Bradley touch screen interface, located outside of the isolator.

The Lyophilizer is of sanitary design with all VHP compatible materials of construction. There are four shelves with a total of 14.2 sq. ft. of area. The unit has bottom-up hydraulic stoppering. It is steam sterilizable and rated for full vacuum. There are a series of spray nozzles, which are connected to a clean in place system (CIP). There is an external condenser with 12 sq. ft. of surface area. It is capable of achieving -55^{o}C on the shelves, and -70^{o}C on the condenser plates. The unit is remote operated using a personal computer (PC). It is fitted with a center hinge, to facilitate opening the door within the isolator.

Figure 4: M & O Perry Filling Machine

The filling, transfer and lyophilizer isolators (figure 6) are located in the filling suite (room 920). Room 920 is a net positive to the lyophilizer mechanical room and the adjoining fermentation suite. It is negative to the gowning room 925, which acts as an airlock between rooms 924 and 920. Each isolator operates at a net positive to the room and the filling and lyopnilizer isolators are both positive to the transfer isolator (Filling isolator = 0.25" w.c., Lyophilizer isolator = 0.25" w.c., Transfer isolator = 0.20" w.c.).

Process Flow

The process begins with the cleaning and surface decontamination of all isolators. The gloves are tested and cleaned. The unit is set-up for the particular size of vial, stopper and cap. Each unit is then loaded with the necessary equipment and decontaminated with vapor phase hydrogen peroxide.

VHP Decontamination

The Transfer Isolator contains the wrapped-vials, environmental monitoring plates, extra gloves, and waste bags. The unit goes through its dehumidification, conditioning, sterilization and aeration phases, using an Amsco VHP 1000 hydrogen peroxide generator. This operation is performed at least 24 hours before a scheduled filling to allow aeration of the VHP to acceptable levels (<0.1ppm).

The Filling Isolator is prepared for decontamination by fitting each of the RTPs with a false container (a beta flange with a polypropylene bag affixed). This enables the decontamination of the gasket on the alpha door. The temperature is raised to about >90^{o}F and the unit goes through the dehumidification, conditioning, sterilization and aeration phases. This operation is performed at least 48 hours before a scheduled filling to allow aeration of the VHP to acceptable levels (<0.1ppm).

The lyophilizer isolator is decontaminated for a cycle with the lyophilizer door opened to decontaminate the door gasket. At the completion of the first cycle, the door to the lyophilizer is closed and the lyophilizer is sterilized internally using steam. The isolator is again decontaminated for a VHP cycle with the door closed. The isolator is aerated to acceptable levels (<0.1ppm) as normal to complete the cycle.

Pre-Filling Preparation

The filling siphon and 105mm canister are sterilized by autoclaving. The 270mm Beta canisters, which contain stoppers, caps and weight-check blocks, are also sterilized in an autoclave. The bulk liquid to be filled is attached to the filling siphon under a class 100 laminar flow hood, and stored at the appropriate temperature until needed for filling. These operations are usually performed the day before a scheduled filling.

On the day of the filling, the supervisory control and data acquisition (SCADA) system is set-up for the filling and the particulate monitoring system activated. The equipment in the Transfer Isolator is unwrapped. The particulate count is allowed to settle to <100 cpm @ 0.5µm in Transfer Isolator, and then it is docked to the Filling isolator. The equipment, including

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a portion of the vial trays, is transferred to the Filling Isolator. The 270mm beta canister containing the weight check block is docked to the Filling Isolator and the blocks removed. The canister remains docked to facilitate the removal of the first weight check vials.

Filling

The filling begins with the set-up and calibration of the filling pump. The lines are primed with the product and several vials are dispensed and placed into the weight check blocks. The weight check blocks are removed through the empty 270mm canister.

The other 270mm canisters are attached to the Filling isolator and the contents (stoppers and caps) removed and placed into the feed bowls. The unit is then ready for filling in the automatic mode.

The non-viable particulate monitoring begins and continues throughout the filling. The viable particulate monitoring takes place during the first hour, middle, and last hour of the filling. The filling lines are primed with product and several vials are filled. These vials are then placed in Teflon vial holders and placed into an empty 270mm canister and removed from the isolator. The vials are gross weighed, rinsed with alcohol, air dried with compressed air and tare weighed. The net weight is calculated and if within the required specification, the vials are filled, and partially stoppered. The capping operation is de-activated during this portion of the filling

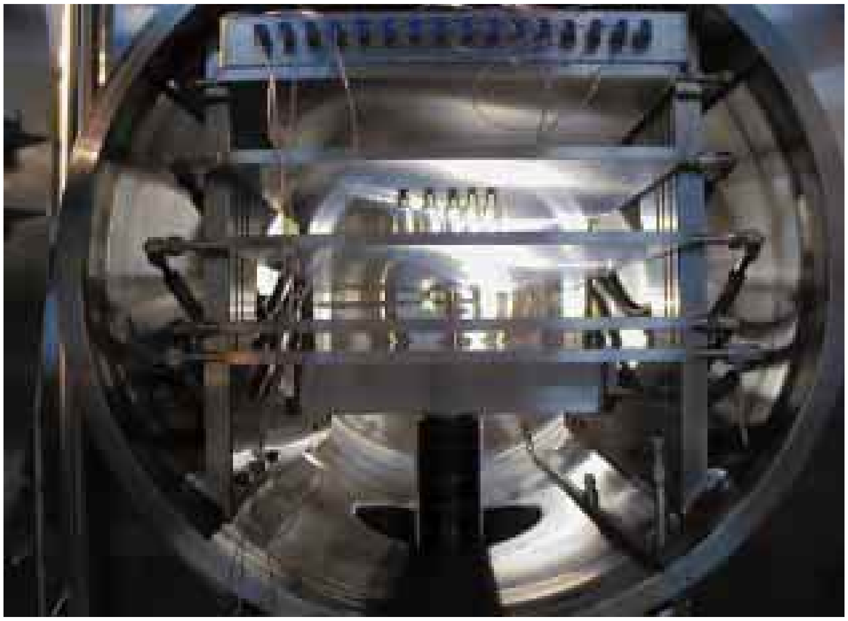
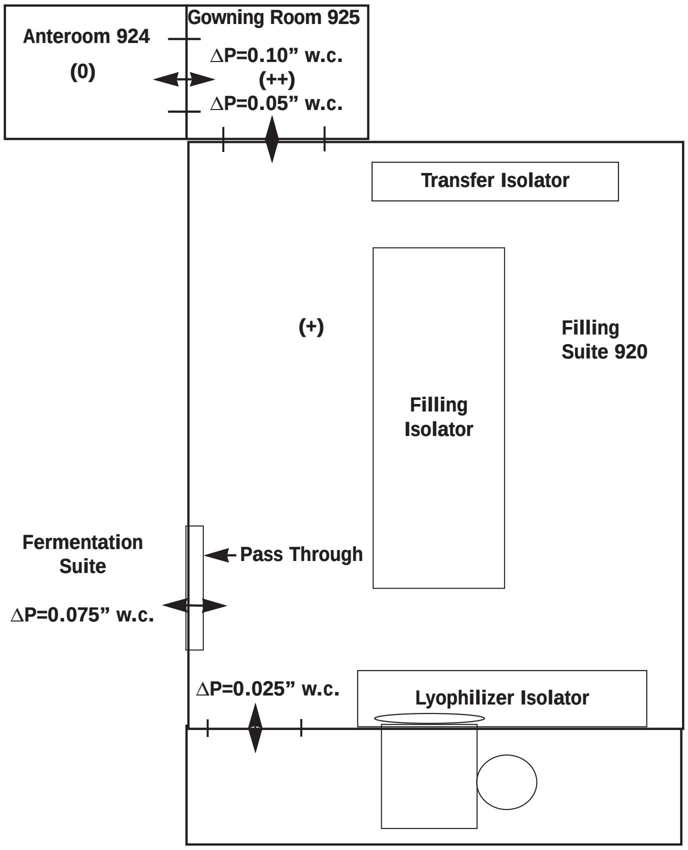


Figure 5: FTS Kinetics Freeze-Dryer

Figure 6: Facility Layout/Differential Pressures



Freeze-drying

The partially stoppered vials are placed on a rack within the filling isolator. The transfer isolator is moved to the opposite end of the filling isolator and docked to the 350mm exit port. The vials are re-racked onto the transfer isolator racks then transfer isolator is un-docked from the filling isolator. The transfer isolator is then docked to the lyophilizer isolator. Next, the vials are loaded onto the lyophilizer shelves and processed through the freeze-drying cycle.

At the completion of the freeze-drying, the stoppers are seated, the vials are re-loaded into the transfer isolator and it is reconnected to the 350mm port at the beginning or the filling isolator. The freeze-dried vials are then loaded onto the filling line, this time the filling and stoppering mechanisms are deactivated and the capping and crimping stations are activated. After all the vials are capped, the filling ends.

Summary

As you can see from the process described above, there are quite a few manipulations required to fill, and freeze-dry our products within multiple isolators. However through careful planning and well-defined procedures, we were able to meet the challenge of producing sterile freeze-dried product in the pilot plant■

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