Advanced Aseptic Pharmaceutical Production in a Scalable Isolator

A Case Study

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PEER REVIEW

Abstract

This article describes a new filling and closing module for syringes and cartridges for biotech and pharmaceuticals, working aseptically in a modular barrier isolator with an automated H_2O_2 decontamination system. The isolator has a modular structure. Both the isolator modules and the machine modules can be combined depending on the production requirements. The isolator modules can be used in aseptic as well as in aseptic toxic production.

Key Words

- Aseptic toxic isolator
- Modular fill-finish
- Small batch
- Advanced filling
- 100 % in-process-control

Introduction

The production processes in the pharmaceutical industry are increasingly changing in the direction of high-quality and highly specialized niche products [1]. Highly potent active pharmaceutical ingredients (HPAPIs) and Antibody Drug Conjugates (ADCs) for example are a new generation of highly active, pharmaceutical products, which are used for the targeted treatment of cancer. Some of these products require occupational safety measures that ensure compliance with occupational exposure limits below 100 ng/m^3 of air in the workplace [2].

Curia Albuquerque, NM/USA, is a pharmaceutical contract manufacturing company which is active in the field of recombinant antibody production and recombinant protein production. As a contract manufacturer, Curia has to be able to respond quickly and flexibly to customer requests and requirements, which is why they chose an isolator system with a filling and sealing module that best meets these requirements.

The innovative and highly flexible production system [3] for biotech and pharmaceuticals is essentially a combination of 2 elements: an isolator and filling and closing modules. The system has been designed to provide utmost flexibility in the production of medications by using one

Authors

Frank Lehmann

Frank Lehmann works in the Industrial Division of SKAN AG, Switzerland. He studied Process Engineering at the University of Applied Sciences in Esslingen (Germany). Now there are more than 20 years of experience in different positions in the cleanroom and pharma industry like product development engineer and project manager. He realized containment projects for different customers all over the world such as aseptic filling lines and toxic isolators. At SKAN, he is now responsible for sales engineering and product management. Further activities are in interest groups like ISPE aseptic group, some publications, and the containment book at Springer Heidelberg.

Thomas Bühler

In 2000, Thomas Bühler started at Bausch+Ströbel Ilshofen to complete an apprenticeship program in business administration. After having finished his apprenticeship in 2002 he started in the international sales and project managing department where he was involved in many high tech projects for the pharmaceutical industry. With his excellent experience in primary packaging machines, he has since then made significant contributions to technological developments and accompanied numerous projects from the first inquiry to the site acceptance test (SAT). Since 2010, he has been in charge of the North American territory as a sales group leader.

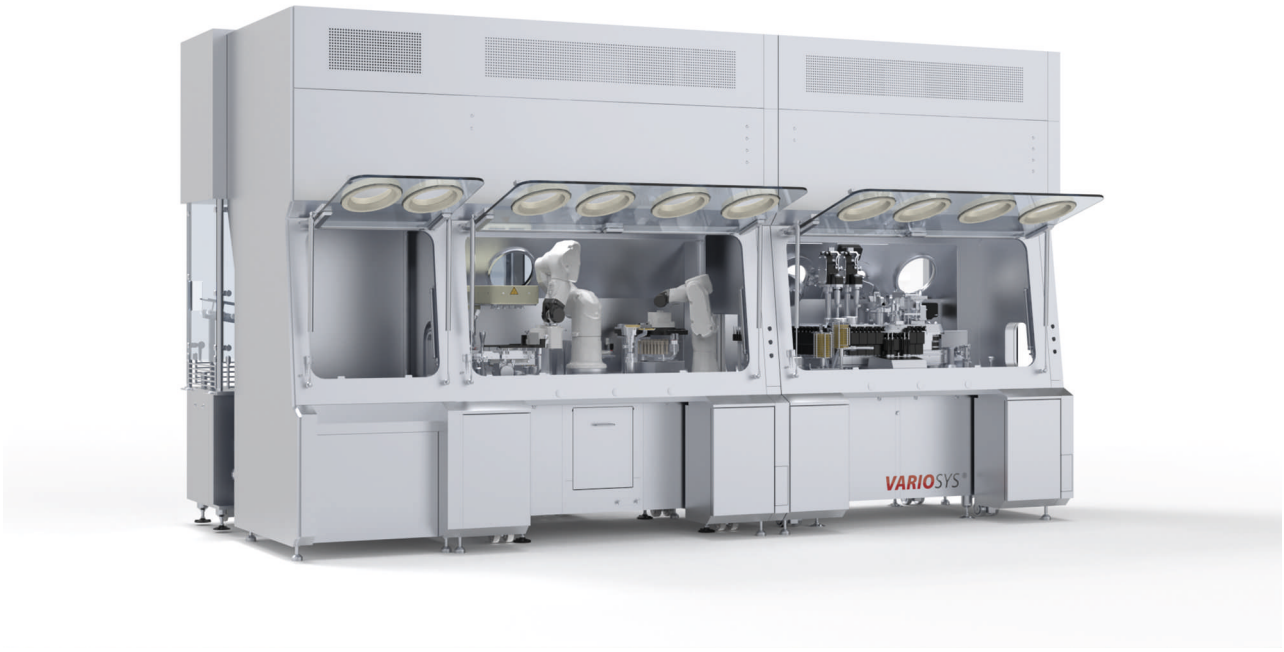

Figure 1: 2 PSI-L Isolators combined with an airlock with denesting and filling modules (source: SKAN AG).

isolator and exchanging the production modules. The machine modules are simply slotted into place, locked into position with power and data plugged in.

When combined with the isolator the modules are ready for production after a short decontamination cycle with hydrogen peroxide (H_2O_2).

The Aseptic Isolator

The isolator module, with 4 glove ports in the front screen, consists of a working chamber made of stainless steel 316 L, open at the bottom and at the back, into which the L-flange with the mounted machines can be inserted from behind, thus completing the working chamber. A pressure-monitored pressure seal connects both chamber parts in a gas-tight manner.

The chamber is ventilated via a terminal High Efficient Particulate Air (HEPA) H14 filter and a catalyst from the ceiling, with a flow rate of 0.45 m/s being achieved during operation. The ventilation unit is largely located in the superstructure of the isolator. A standard ceiling height of 3 m (10 feet) is sufficient for the whole isolator including air handling system. The system takes the required air from the surrounding area through the ventilation slots in the front panel of the superstructure. The surrounding space is defined as a class C (ISO 7) cleanroom. In the ventilation unit, a catalyst that splits hydrogen peroxide into water and oxygen ensures that the air can be released back into the room without any pollutants [4].

In the substructure, in the return air duct, there is a filter cartridge H14 [5] in each side, which holds back possible highly active substances that are processed in the chamber and thus protect the ventilation unit and the catalyst inside (fig. 1).

In the front screen, which can be opened upwards and is held in the upper position by 2 shock absorbers, there are 4 oval glove ports that enable the operating personnel to intervene in the process flow in the event of a fault. Internal LEDs illuminate the chamber inside, the alarm light and the acoustic alarm are also installed on the chamber.

Each module is equipped with a H_2O_2 fogging system [6] for the quick and save decontamination of the working chamber. In addition to the isolator modules, there are airlocks of various sizes and shapes, as well as other systems for transferring new and processed tubs in and out. The airlocks are all equipped with an H_2O_2 fogging system for rapid decontamination, with lock-in times of less than 15 min, being achieved with depletion of *Geobacillus stearothermophilus* spores in a quantity of 10^6.

A Programable Logic Controller (PLC) controls all functions and monitors all data created by the sensors of the isolator. In the aseptic isolator the following data are measured:

- Differential pressure vs the surrounding room, to guarantee that even in the case of a leak the barrier is intact.
- Temperature, to monitor the temperature during the filling process. With a cooling or heating unit in the air handling system,

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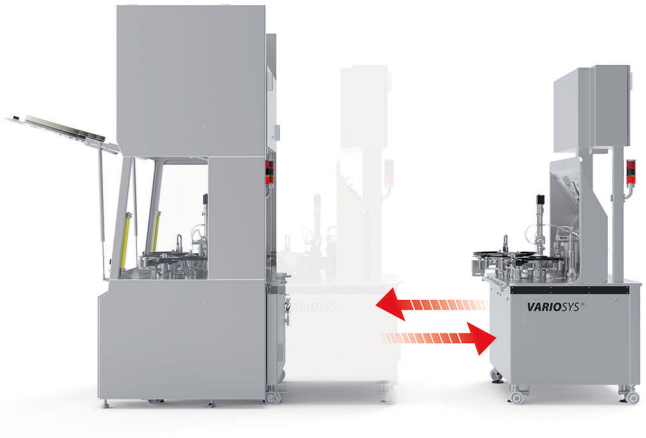

Figure 2: Changing of process equipment in the isolator (source: SKAN AG).

the temperature can be adopted to the process requirements.
- Relative humidity, to verify the start point of the decontamination at 20 % rH.
- Air flow speed, to verify the ability of the airflow to remove particulates created during production.
- Particulate, to verify Class A environment.

Additionally, to the physical parameter, a monitoring program to control the status "free of germs" has to be established [7].

The front design is optimized for the use of the isolator in a cleanroom class C. It is easy to clean inside and outside because it was designed to keep both the aseptic area and the outside free of cracks and crevices as much as possible. The service covers in the upper area of the isolator are held closed by magnet locks, which enable a smooth outer surface of the service cover [8].

Each isolator module can be combined with another from the series or with a lock. Depending on the production process, lines can be put together so that all the necessary process steps for the production of a sterile product can be performed fully automatically step by step under cleanroom conditions (fig. 2).

For example: When the vial filling is completed the inflatable gasket is deflated and the module on casters is coming out. As soon as the vial module has left the isolator, the syringe filling module can come in. After inflating the gasket, the isolator is ready for decontamination with H_2O_2.

Nest Processing

Pharmaceutical manufacturers are increasingly using Ready to Use (RTU) containers, particularly in processes such as small batch manufacturing of precious products. This eliminates the need for cleaning and sterilizing syringes, vials, and cartridges, as well as the validation of these processes. The nested containers in tubs are delivered directly to the dosing process in special packaging. The filling line can be used in combination with hand-

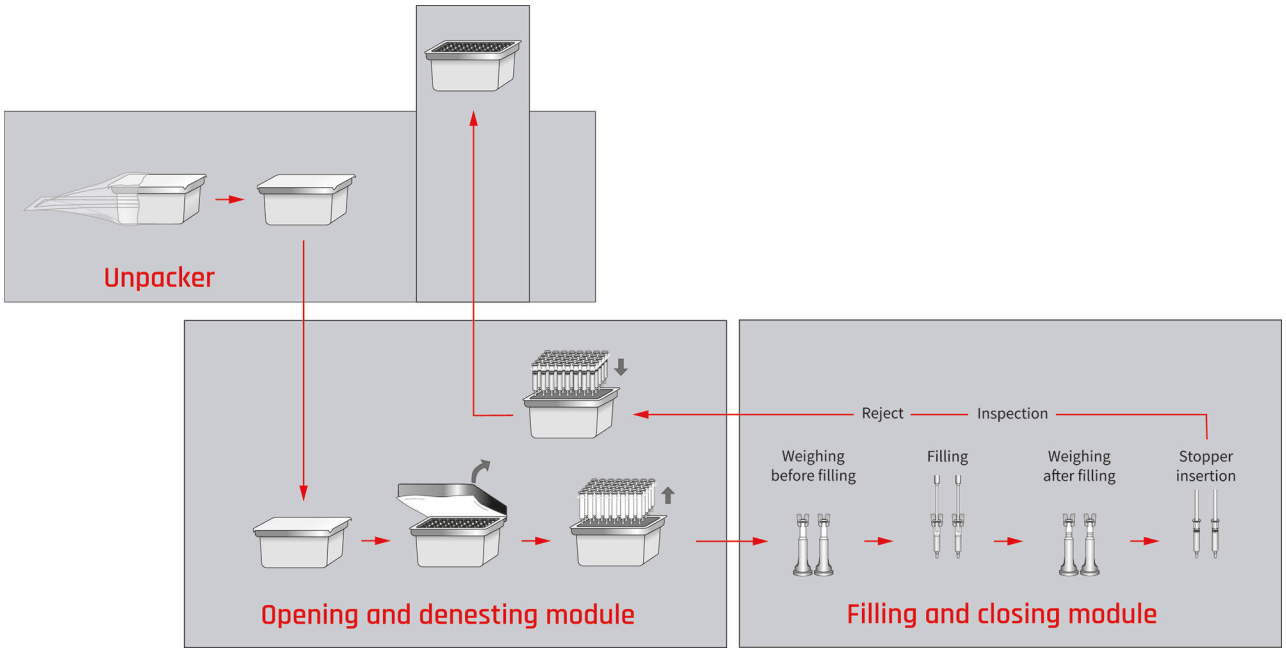

Figure 3: Tub processing scheme (source: the authors).

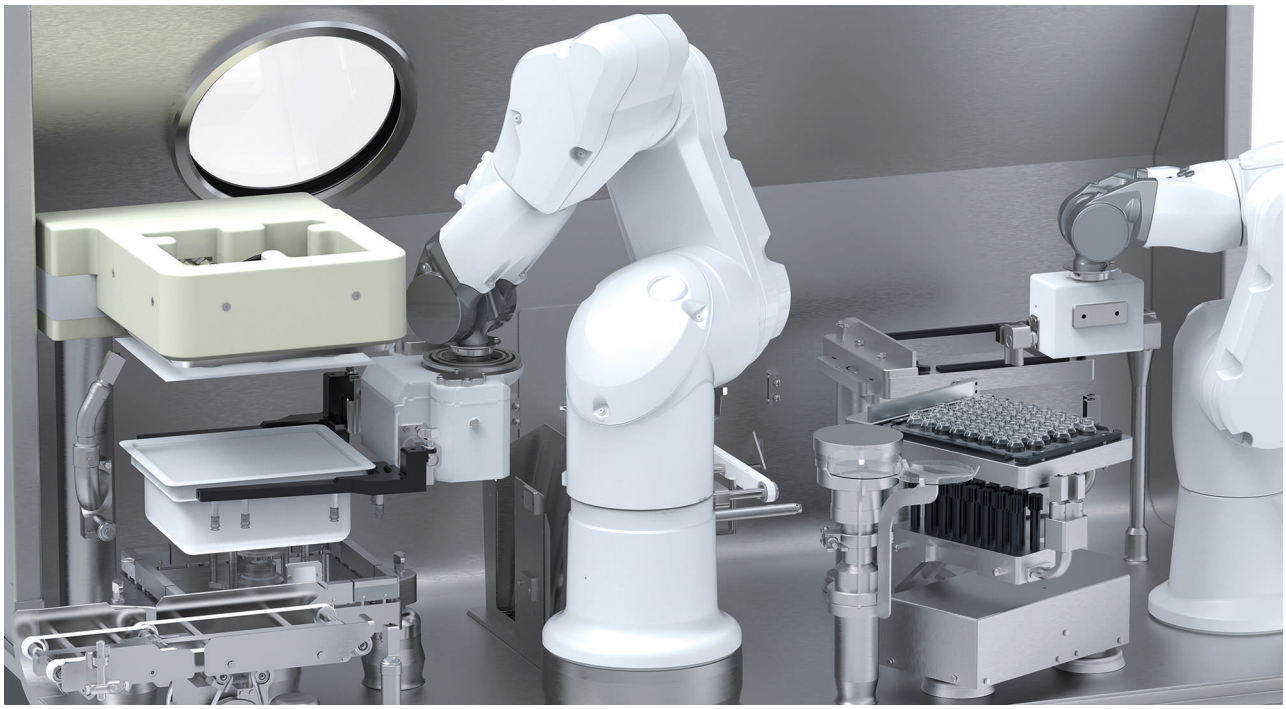

Figure 4: Isolator for the denester with 2 robots (source: Bausch+Ströbel).

ling, filling, and closing modules to guarantee efficient processing and compliance with all regulations applicable to aseptic production.

The increasing process automation presents manufacturers and suppliers with new challenges, also in the area of plant safety. In order to ensure a high process reliability, a special option for the integration of robots within the isolator is offered (fig. 3).

The Unpacker

The syringes, vials and cartridges are delivered aseptically in so-called tubs (white plastic boxes sealed with Tyvek® foil), which are packed in 1 or 2 PE bags and sterilized in them. The tubs with the syringes, vials or cartridges are introduced into the aseptic area of the isolator without the operator touching the sterile tub. The tubs in the bags are placed onto the unpacker [9] manually by an operator. The operator takes the tub, which is sterilely packed in a foil, and inserts it into the unpacker. The front end of the bag is manually clamped in a holding device. Then the operator lays the back end of the bag flat on the cutting tool. Now the airlock opens the mouse hole and gives the way for the tub through to the isolator.

With the two-hand operation, it cuts open the bag. The cutting bar then lowers, opening the way for the tub to enter the mouse hole. A sliding device now pushes the tub with the open bag directly into the mouse hole. A suction device lifts the top of the bag and the tub is transferred through the air lock in the isolator. The inner rotation of the air lock largely closes the mouse hole in terms of ventilation.

The empty bag is now automatically pulled back and the cutting tool moves back to its starting position. The clamp opens and the empty bag and the portion left by the cutter are removed and deposited in a waste bin manually. The system is now ready to introduce the next tub into the isolator.

The Denester

The next station of the line is the denester [10]. In the isolator there is a 6-axis robot that places the tub from the flat belt, where it arrives after passing through the rotary air lock, onto the lifting device that guides it to the heating frame [11]. The task of the heating frame is to heat up the glue in the Tyvek film that seals the tub in a sterile manner and to liquefy it to such an extent that the film can be pulled off by a suction device.

After heating, a suction device holds the foil while the tub is lowered. This separates the tub and the sealing film. In the next step, the robot places the now open tub in a position in which the cover sheet, which protects the containers, is removed with another suction device. At the same time, the lifting device at the position of the heating frame picks up the Tyvek film on the heating frame with the lifting device. It is then discarded by the robot into a waste bin below the work level.

The robot places the nest with the syringes from the tub in a station where the syringes are removed row by row by the second robot in the isolator. A lifting device in the

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station lifts the containers so that the robot can grip them. The robot transfers the containers row by row to a transfer device which carries the containers to the main transport of the filling module (fig. 4).

The processed tubs are ejected through the second airlock where they are again filled with a full nest of full syringes or cartridges. When vials are processed, they will be transferred from the filling module to a downstream lyo or capping module.

The speed of the denester matches up with the filling modules.

If robots are used in the isolator, the steel work is enforced with upgraded hinges and active interlock in the middle to protect the operator from robot accidents. Special covers close the glove ports during robot operation. The front door is a reinforced variant for use with robots [11].

Filling and Closing Operation

The filling and closing module enables the processing of syringes, cartridges and vials with integrated 100 % in-process-control (IPC) without loss of performance on one single module. All filling systems used in pharmaceutical production can be deployed [12].

The containers are inserted into the transport system of the machine through the transfer table. From there they are first transported to tare weighing, then to the filling station with advanced fill. Advanced fill means a loss-free approach and production. During start up and run empty the container stands on the gross scale until the defined filling quantity is reached in the first container. During production, the containers are first weighed on the tare scale before they are filled. After filling, the containers are weighed again using the gross scale. In case of underfilling of the container, it is possible to add more.

The syringes and cartridges are then sealed with a plunger stopper. The position of the plunger stopper is then checked by a vision system. If an incorrectly placed piston stopper is detected, the object is rejected in the reject ejection. The "good objects" are transported back to the transfer station and from there transferred back to the denester. Vials will be stoppered and transferred to the downstream lyo or capper.

Back on the denester, the robot places the objects back into the nest. The full nests are then returned into the tubs by the robot and these tubs are transported back from the denester to the unpacker through the second air lock. The full tubs with the filled objects are output via the roller conveyor.

The filling and closing machine can process a wide range of syringes from 0,5–10 ml objects. The targeted output is up to 4 300 objects per hour.

With the self-priming and run empty function without product loss, only the last container may need to be rejected.

Summary

The pharmaceutical industry in western industrialized nations is moving further and further away from the mass production of tablets and liquids towards high-priced products. These products are only manufactured in small batch sizes, sometimes also patient-specifically. Small batch sizes mean frequent changes in pharmaceuticals and packaging. Mechanical engineering has to take this more and more into account. The machines for filling and sealing liquid medicines are becoming smaller and more flexible in practice. With the "advanced fill" and the "run empty function", product loss is minimized.

The aseptic environment, the decontaminable isolator, also decreases with the size of the filling machines. In order to achieve high flexibility with stable cost, the isolator and the machines are coordinated in such a way that different filling modules can be used in one isolator one after the other. In addition, it is possible to combine isolator modules and transfer units as desired, which means that almost any production requirement can be met.

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