A New Concept in Aseptic Filling: Closed-Vial Technology

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The closed vial has been developed to improve aseptic filling quality and to reduce process complexity. A ready-to-fill closed vial consists of a sterile vial provided with the stopper secured in place. The vial is filled by inserting a non-coring needle through the stopper, which is then resealed by laser.

Aseptic filling has been well established for several decades but regulatory requirements have become more and more restrictive over time. For example, authorities have requested increased environmental safety in the filling area, with very strict requirements regarding eliminating potential contamination agents and reducing partides, in addition to revising product formulations to eliminate preservatives. These recommendations have led to two major improvements: better air quality control to reduce contamination risk and new container designs.

Containment technologies reduce the risks associated with the human presence in Class 100 cleanrooms. The isolator appears to be the best solution in terms of quality, although it is the most complex for pharmaceutical manufacturing, especially for conducting multiple and difficult validation experiments, performing controlled vapor-phase hydrogen peroxide sterilization, maintaining delicate pressure balances, and controlling the complex airflow patterns generated in the closed environment.

Faced with the complexity of using isolators, manufacturers have developed open barriers, particularly the restricted access barrier system (RABS), which consists of a barrier system with hard walls (allowing access only through gloves), but which is in fact an open system. The RABS is based on the principle of a regular air flow pushing all possible sources of contamination to the bottom and then outside the barrier without any air recirculation. The sterility assurance level inside a RABS appears to be similar to that of an isolator.

Since the classical ampul was introduced, several new container designs have been configured such as the vial, the cartridge, and more recently, the prefilled syringe. All these containers have been developed in response to one key concern: ease of use throughout the supply chain. The vial, for example, is a more-solid container with a reduced risk of generating glass partides, and the prefilled syringe eliminates handling during drug administration. Nevertheless, because all these containers remain open during aseptic filling, they do not succeed in significantly reducing the risk of contamination from the environment.

This article presents a new concept: closed-vial technology. This technology is based on a vial that is supplied closed and sterile and therefore ready-to-fill. This sterile vial, which functions like a mini-isolator, is filled in a Class 100 environment inside a RABS.

Figure 1: The five vial elements are (from bottom to top): the bottom ring for mechanical stability and processing; the vial body containing the liquid; the stopper that can be resealed with a laser; the top ring, which ensures closure integrity between the vial body and stopper; and the flip-top cap to protect the piercing area.

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Figure 2: Closed vials are available in sizes ranging from 2 to 100 mL, all with the same cap size.

The closed-vial concept

The principle of the closed-vial concept can be summarized as follows:

- The body of the closed plastic vial is made of cycloolefin copolymer (COC), a plastic material that can be molded into shapes that are not feasible with glass and that allow for tighter seals between parts of the vial, thus improving closure integrity.
- Closed vials are clean and do not require washing before filling. The vial body and the stopper are molded and assembled in Class 100 environment, leading to extremely low particle levels inside the container.
- The vial is sterile. After assembly, the closed vial is sterilized in a gamma-irradiation unit to secure the absence of vial contamination, eliminating the vial washing and depyrogenization step in the filling line.
- In the filling process, a needle penetrates the closed vial through the stopper. After the liquid is delivered, the needle's path is resealed with a laser beam to restore closure integrity. Stopper integrity can be achieved because the stopper is made of a thermoplastic elastomer, which can remelt and fuse when the temperature is increased.

The closed vial

The closed vial consists of five major elements (see Figure 1): the vial body, which can hold 0.5–100 mL of liquid (see Figure 2); the stopper, which is pierced by the needle and then resealed with a laser; the top ring, which provides a tight seal between the vial body and the stopper; the bottom ring, which facilitates mechanical processing; and the flip-top plastic cap, which protects the piercing area.

The closed vial body is made of COC, a plastic that has already been used to contain parenteral drugs (*e.g.*, the COC prefilled syringe) and that provides excellent resistance, minimized transmission rates for water and various gases, and excellent optical performance. COC is hydrophobic and therefore does not require additional siliconization to allow easy liquid collection.

COC can be molded to achieve several desired properties in the vial body. In particular, right-angle snap fits have been designed to ensure that the vial's parts fit tightly together, and a confidence ring has been placed around the top of the vial body to create a concentrated pressure contact point between the stopper and the vial body. These two elements ensure excellent closure integrity for the assembled vial.

The stopper is made of a thermoplastic elastomer that can absorb laser energy to melt and fuse without burning. After it has cooled down, the mechanical properties of the melted material are identical to those of the initial material (which was also melted during the molding process). The stopper shape has been designed to minimize dead volume (no recess area exists) and to provide a large piercing area for the practitioner, facilitating liquid collection and minimizing the risk of injury when the needle is inserted. The stopper also is highly flexible, allowing it to maintain close contact with the needle during the filling process. Both the vial body and stopper materials meet USP Class VI criteria to ensure patient safety.

The vial's top ring ensure a tight seal between the vial body and the stopper by leveraging the property of right-angle snap fits described above. These snap fits provide strong closure integrity without requiring significant downward pressure during assembly, which would weaken closure integrity.

Figure 3: The sterile, ready-to-fill vial is delivered uncapped (left). After filling, the vial is capped (middle) inside an isolator. To use the vial, the central part of the flip-top cap is removed (right), exposing the large puncture area that has been kept sterile by the circular rib.

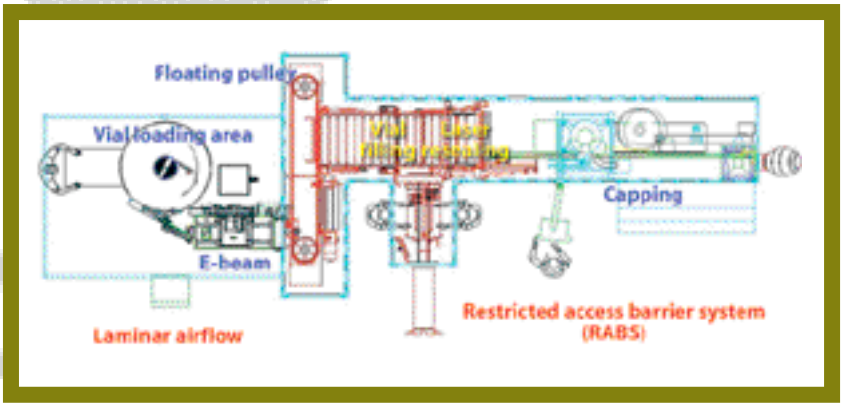

Figure 4: An overview of a production line for closed vials. First, under soft-wall laminar airflow, boxes of vials are opened mechanically on the loading table, and the vials' top surface is sterilized by an electron beam. Then, in the RABS, the vials' linear movement is converted to a parallel movement by a floating pulley. The vial filling and the laser resealing are performed on the transport bars, and then the vials are capped.

Figure 5: Overview of a clinical machine with the loading and electronic beam steps conducted under a soft-wall laminar airflow (on the left) and the filling steps (filling, laser resealing, and capping) conducted in a restricted access barrier system (RABS, on the right).

The bottom ring helps stabilize the vial during line loading, but its key role is to allow the vial to be held tightly with clamps during the needle withdrawal step at the end of the filling process. Without such a tight hold, it would be very difficult to withdraw the needle without lifting the vial.

Finally, the sterilized cap protects the piercing area until the flip-top cap is opened. This protection is obtained by a circular rib that tightly covers the stopper's surface. The cap is installed inside a barrier isolator to maintain aseptic Class 100 condition below it (see Figure 3).

The method of manufacturing closed vials also is new. Closed vials are molded and assembled in a Class 100 environment to minimize the number of particles present inside the vial after production. The manufacturing principle consists of the following five steps.

Molding the vial body and the stopper. Two molding machines are installed in a Class 100 environment; material is injected directly from plasticating screws located outside. After molding, the vial body and the stopper are picked up by robotic arms, which are used to manufacture microelectronic parts and therefore are designed to maintain Class 10 environment conditions.

Assembly. The two robotic arms are placed across from each other. A stopper is inserted into the vial with light pressure and a slow, precise motion. The assembled vial is then transferred to an adjacent Class 10,000 cleanroom for further processing. The fact that 32 vial bodies and 32 stoppers are molded and assembled at the same time allows the use of slow machine movements during their manufacture to minimize particle generation while achieving satisfactory output levels.

Figure 6: Overview of the filling area in a clinical line. Inside the RABS, a wheel moves the vials to each filling step: the filling with the needle piercing the stopper (top right); the resealing of the stopper with a laser (top left); and capping (bottom left) before the vials exit the RABS.

Addition of rings. The top and bottom rings are applied by simple pressure.

Packaging. The vials are placed in corrugated polypropylene boxes and double-wrapped in polyethylene bags.

Sterilization. A complete pallet of vials is transferred to a gamma sterilization unit and a minimum of 25 kGy are delivered.

The closed-vial filling line

The setup of the closed-vial filling line is illustrated in Figure 4. The filling process consists of five steps: the opening of the polypropylene boxes that contain the vials; sterilization by a miniature electronic beam directed at the top surface of the vial; vial filling by inserting a needle through the stopper; resealing the stopper with a laser; and capping. The two first steps are conducted under a Classic laminar airflow, and the last three are performed in a RABS.

The filling line can be set up in one of two formats. The clinical format (see Figure 5) has a filling capacity of 1500–3000 vials per hour, with one or two vials processed at a time. In this setup, filling operations are performed on a wheel that stops at each step (see Figure 6). The commercial production setup, in turn, has a filling capacity of 10,000–40,000 vials per hour, depending on the number of vials processed in parallel (6, 12, 18, or 24 vials).

To load the line, a mechanical system allows the vial boxes to be opened without the operator's hands coming close to or above the vials. This line-loading operation is performed under laminar airflow with soft walls to allow access if necessary.

Then, just before the vials are transferred to the RABS, a miniature electronic beam sterilizes the critical top surface of the vials. This miniature electronic beam is very small (it is a 60-cm cube weighing 120 kg, including lead protection) and delivers a dose of 25 kGy. The radiation penetrates the stopper to a depth of 30 µm, eliminating the shadow risk.

The next three filling steps are conducted within the RABS. First, a needle pierces the stopper to dispense the liquid drug. The needle has been designed to minimize particle generation (a noncoring pencil point is used), to inject the liquid smoothly (at a 30° angle through holes in the needle wall), and to allow excess pressure to vent (grooves allow gas to flow out of the vial).

Next, a laser reseals the pierced stopper. A laser beam with a flat-top energy curve is applied to reseal an area significantly larger than the piercing path. The use of a flat-top energy curve allows equal energy distribution to avoid the risk of burning the middle and not resealing the sides. The stopper surface temperature increases to 160 °C during a very short period, but the inner face of the stopper only reaches 38 °C for a few seconds,

so the product is not affected by the temperature increase.

The last step is capping, which also is done in the RABS to entrap aseptic conditions at the stopper surface. The circular rib ensures closure integrity.

Key advantages of the technology

The closed-vial technology provides four major advantages:

- Better sterility assurance combined with a lower level of particle contamination for patients. The closed vial is never exposed to air and therefore has properties that are similar to those of an isolator that is only disturbed during needle penetration. The quality of the vial manufacturing and the filling process ensure very low levels of particle generation and glass-free manufacture of the vials.
- Less investment is required by pharmaceutical manufacturers. The closed-vial filling line, which is simpler than a classical filling line because several steps (*e.g.,* washing, passing vials through a hot-air tunnel, and stoppering) are eliminated, is also significantly cheaper compared with a similar-capacity process conducted under an isolator. In addition, other production costs can be eliminated (*e.g.,* the water for injection [WFI] loop for vial washing) or reduced (*e.g.,* cleanroom space to install the line can be reduced by more than half compared with classical glass-vial filling lines). Eliminating WFI production, including the associated validation and monitoring costs, is the major driver for cost reduction. Other sources of cost reduction include reducing energy consumption, employing fewer workers, increasing productivity, and reducing dead volume in the vial.
- Operator safety is improved throughout the supply chain. Closed vials are filled in a confined environment (a RABS), eliminating the risk of spillage outside the RABS that could expose operators to potent or cytotoxic drugs. In addition, the mechanical resistance of the plastic vial minimizes, and practically eliminates, the risk of breakage during filling, labeling, and packaging and throughout the entire the supply chain to the healthcare practictioner's office.

Conclusion

Because of its advantages, the closed-vial technology is likely to become a standard for pharmaceutical aseptic filling processes. The technology not only improves quality for the patient, but also significantly reduces the complexity and cost of filling operations for manufacturers.

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