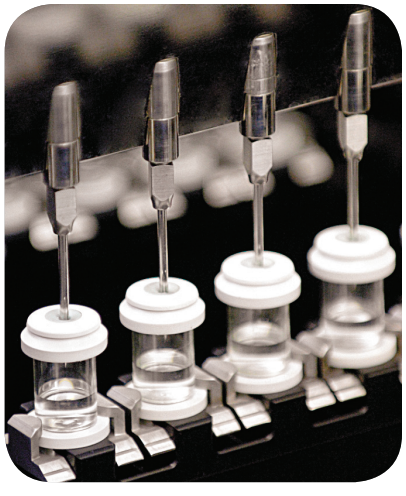
Using Closed-Vial Technology

In Aseptic Filling

Benoît Verjans



The pharmaceutical industry is continually looking for more robust and less complex aseptic filling solutions. Closed-vial technology is an alternative to traditional glass vial filling that reduces the risk of contamination for the patient, simplifies the filling process, and provides easier handling for healthcare providers. The author describes the closed-vial manufacture and filling process.

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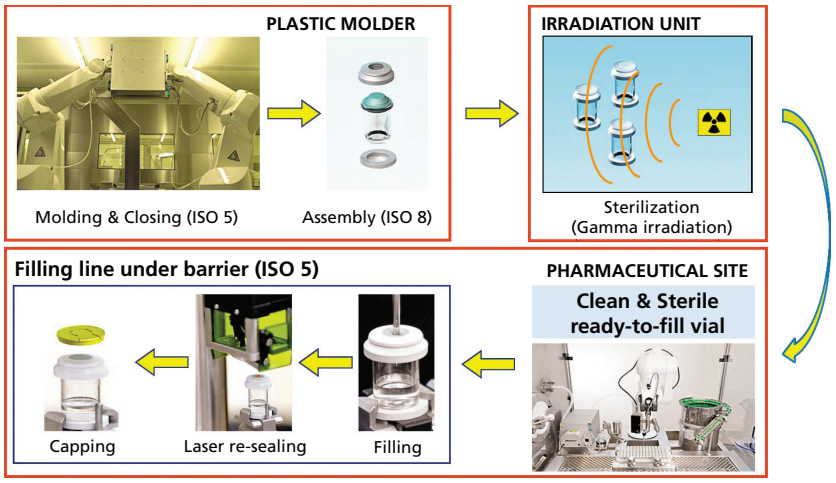
Aseptic filling remains a risky process with multiple contaminations occurring each year that have serious consequences. Analysis of an outbreak database shows that, among 1537 patients contaminated by parenteral product from 1990–2005, the mortality rate was 15%. While the majority was due to product preparation at the hospital pharmacy or the practices of the hospital staff, 20% of these contaminations were due to the pharmaceutical manufacturing process (1).

This high contamination risk leads authorities to regularly reevaluate their requirements, thus making aseptic filling one of the most complex processes in the pharmaceutical industry. A continuous improvement approach, however, has led to major innovations, and the rate of contamination has been significantly reduced during the past 50 years. The innovations listed below involve both the container and filling technologies:

- The vial emerged as the standard primary packaging and replaced the old-fashioned ampoule, which had higher risk of breakage, contamination through small cracks, and glass particle generation when the ampoule was opened.
- Better practices have been developed for aseptic filling, such as personnel gowning, equipment/process design, and environment monitoring.
- Physical barriers have been created between the operator and the filling area. Initially the barrier was made from simple walls but now includes the isolator concept. Isolators prevent direct contact between the operator and the filling process, including the bulk products, containers, and product contact parts (2).
- Process analytical technology (PAT) was developed to perform on-line checks on product quality. Checks include the classical weight check as well as newer checks such as particle inspection and leak detection.

These innovations improve product quality but also add complexity to the aseptic-filling process. As a result, aseptic filling is expensive, demands complex quality control, and has many potential opportunities for mistakes. Closed-vial technology, however, can improve product quality and simplify the aseptic-filling process (3, 4).

Figure 1: Production cycle of a closed vial from molding the container to filling and capping.



Closed-vial process summary

Figure 1 shows an overview of the production and filling of closed vials, which occurs at three separate facilities. The vial is molded and assembled in an ISO5 cleanroom and rings are added. At a separate facility, the vial is sterilized by gamma irradiation, which leads to a clean, sterile, ready-to-fill vial. The vial is delivered to the pharmaceutical filling site for filling. In this process, a needle punctures the stopper and dispenses the liquid. The puncture trace is then resealed with a laser to restore the closure integrity. Finally, the vial is capped with a snap-fit, polyethylene cap.

Advantages of closed-vial technology

Closed vials can offer three main advantages compared with traditional glass vials.

Increased patient safety. In glass vial technology, the vial stays open for more than 30 minutes between exiting the depyrogenation tunnel and stoppering. Stoppers may remain in a stopper bowl for several hours, in which direct contact with surfaces increases the risk of transferring a contaminant to the vial. A closed vial, however, remains permanently closed except during needle penetration, thereby reducing the risk of contaminant entering the vial by two logs (5).

Simplified manufacturing process. The closed vial is delivered clean and sterile, allowing the pharmaceutical manufacturer to eliminate container-component preparation, including water for injection (WFI) washing, steam sterilization, and hot-air depyrogenation. High speed stoppering and aluminum cap crimping are also eliminated. The break-resistant polymer material reduces vial breakage inside the filling area and during the supply chain.

Easier handling for healthcare professionals. The closed vial's cap can be easily opened by breaking small polyethylene bridges. Piercing is facilitated by a large piercing area. Liquid collection is complete due to the absence of recess areas in the stopper design. Finally, the vial does not break if dropped. A market study performed for Aseptic Technologies in 2007 found that among 246 professionals (i.e., medical doctors, nurses and hospital pharmacists), 87% preferred the closed vial (Crystal Closed Vial, Aseptic Technologies) and 7% preferred the glass vial. The most often cited reason for preferring the closed vial, as shown in Figure 2, was that it is easy to handle.

Closed vial container design

The following sections describe a typical closed-vial container and the manufacturing and filling process. These sections also explain how the container design and the manufacturing process provide a solution for challenges in aseptic filling.

Vial body. In this closed-vial system, cyclo-olefin copolymer (COC) (Topas, Topas Advanced Polymer) was selected for the vial body because it does not create high particle levels during molding. Low particle generation is a requirement for avoiding WFI washing after manufacturing in an ISO5 clean room. COC is already used in some injectable products (Metalyse, Boehringer-Ingelheim), and is widely used in blister packaging. COC is a clear, transparent polymer that allows good light transmission and has a high barrier to water vapor. In addition, it can be gamma-irradiated without degradation or a visible change of color at standard irradiation doses. COC is shock resistant, which reduces the risk of loss during production and transportation.

Polymer molding has greater design flexibility compared to glass forming. Several features are shown in Figure 3. In particular, the tightness of the vial is ensured under all conditions, even under the low temperatures of liquid nitrogen.

Figure 2: Results of market survey of healthcare practitioners showing the reason for their preference of closed over glass vials.

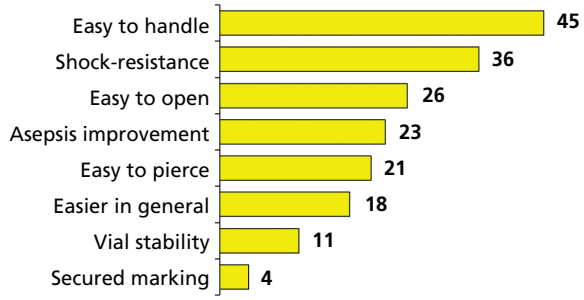


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Figure 3: Detail of closed vial container design showing features not available in glass vials.

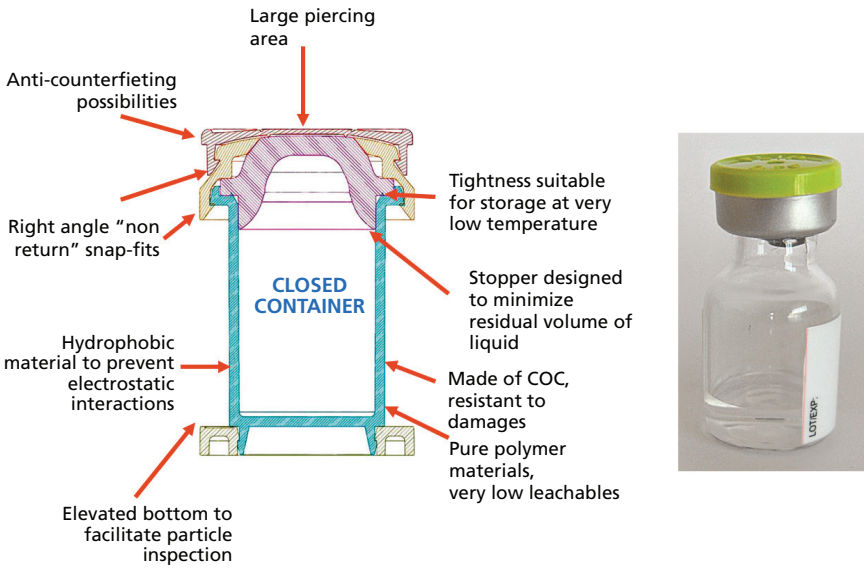
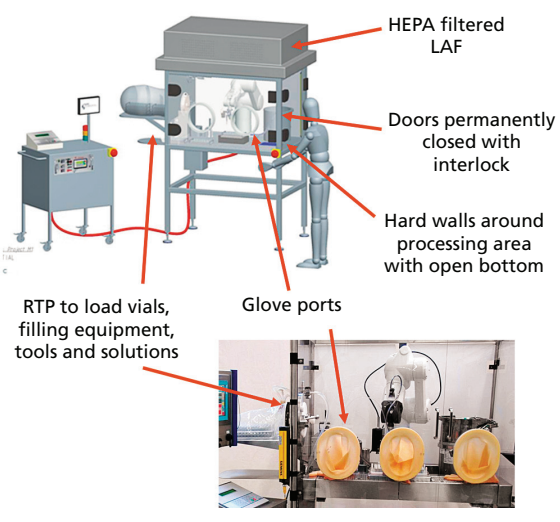


Figure 4: A closed-vial filling system surrounding a robotic filling line.



Stopper. The stopper should reseal when heated by the laser to ensure reclosing of the puncture trace. The stopper must be able to absorb the laser energy with a good profile of heat distribution. Second, the stopper should be highly flexible and easy to pierce with a large needle without generating particles of significant size or amount and without material loss. Third, to ensure optimal resealing process after liquid fill and after lyophilization, the stopper should have good elastic memory. It is crucial to have both sides of the piercing trace in tight contact to ensure optimal laser resealing. Finally, the stopper material used should not release deleterious leachables. A thermoplastic elastomer (TPE) has these features, and the polymer can be engineered using a color pigment to ensure optimal absorption of laser energy.

Vial head. The vial head is equipped with a top ring to secure the assembly of the vial body and the stopper, as shown in Figure 3. In this design, the vial head has also been equipped with a snap-fit, high density polyethylene (HDPE) cap. This design eliminates the complex and particle-generating crimping process necessary with an aluminum cap. A small rib on the internal surface of the cap adds closure integrity by isolating the central part of the stopper from the environment until use by the doctor.

Closed-vial manufacturing process description

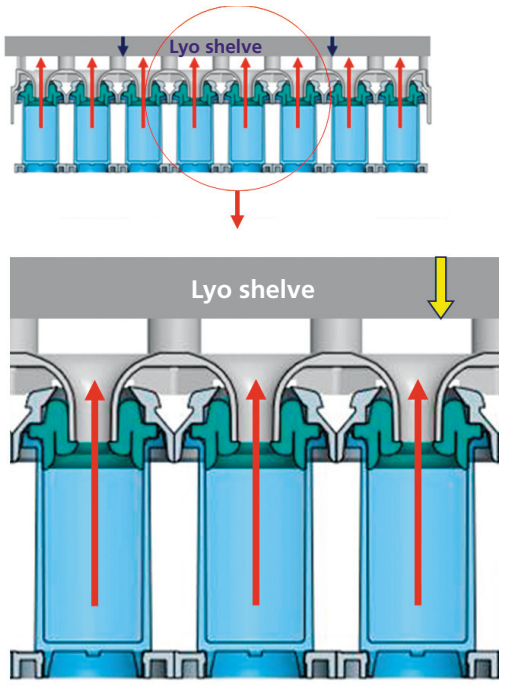
The major innovation of the closed-vial technology is the production of the vial components in an ISO5 clean room. As a result, the components are ready-to-use and do not require the complex cleaning process that is mandatory for glass vials and rubber stoppers.

Ensuring cleanliness. To ensure the cleanliness of the vial components, various conditions have been imposed on the process. First, the molds should not contain lubricating additives that are sometimes used to ease removal of the part from the mold. Second, once the room is qualified for operation, the operators cannot enter. Vial conveying must be fully automatic and should not create particles above the specified level. Vial transportation is performed by robots as shown in the first step of Figure 1. Such robots are already widely used in the ISO4 or ISO3 cleanrooms in the electronic industry as well as in the pharmaceutical industry for applications such as syringe filling.

Because the robots can achieve high precision, the stopper is designed to come straight to the vial body, which avoids the presence of a recess area when the vial is upside-down for liquid collection. Therefore, all the liquid will reach the bottom of the vial and be collected (see Figure 3). As a result, vial overfill can be reduced, thus leading to significant savings of API.

Ring assembly. After assembly of the two components, top and bottom rings are added. Each step is checked by visual

Figure 5: In a lyophilization chamber, shelves push on the penetrator plate to reopen the piercing trace and allow sublimated water to evacuate.



sensor control or mechanical challenge before moving to the next operation. This complete PAT ensures that the vial is fully and properly assembled.

Sterilization. Because the TPE used for the stopper is sensitive to heat, the only classical sterilization procedure suitable for the closed vial is irradiation. Gamma irradiation is preferred to beta irradiation because it is available worldwide and can process a complete pallet at once.

Filling methods. Closed vials are provided ready-to-fill. The five most frequently used methods for loading are:

- Wrapped vials are loaded into the filling area before sanitizing so the external part of the bag is sanitized along with the equipment. This method is used for very small batches (i.e., maximum of a few hundred vials).
- Beta-bags are connected to rapid transfer ports. This method is used for small batches (i.e., a few thousand vials) with robot filling lines using closed vials in racks.
- Vials enter through vaporized hydrogen peroxide airlock with sanitization of the last bag. This method has a limited capacity, due to either the small size of the airlock or the long cycle time, and is therefore efficient for low-capacity filling equipment.
- Vials entry through airlock cascades from an ISO8 to ISO5 environment, using robots to perform automatic debagging and box opening. This is used for mid to large scale batches (e.g., 25–200 vials/min.).
- Vials are removed from bags and boxes, followed by e-beam sterilization of the stopper top surface. This method is used for very large batches (i.e., up to 600 vials/min.).

Using ready-to-fill vials eliminates component preparation and thus has a huge impact on the entire facility. Equipment for vial washing, a hot-air tunnel, and equipment for stopper washing/sterilization is not needed, and clean room space is reduced. WFI for formulation and equipment cleaning can be sourced from a much smaller WFI loop, or containers may be purchased from external sources.

Another change to the filling process is that a needle must pierce the vial stopper before filling, and the hole must be reclosed after filling. The vial must be held in a fixed position during piercing, filling, and removal of the needle. The vial must also be held in position under the laser head to be resealed, and the laser must ensure complete coverage of the piercing trace, so the laser has a uniform energy beam on a 6 mm diameter surface. After resealing, a snap-fit cap is pressed in place.

Containment

The closed vial acts as a mini-isolator because exposed surfaces are limited to the stopper top surface and the needle. In contrast, in a traditional glass vial, the inside of the vial, the inside surface of the rubber stopper, and the needle are exposed until the vial is stoppered. The closed vial filling system (CVFS) offers a new barrier or containment concept, in which only closed containers are handled (6, 7). The CVFS is suitable for installation in an ISO8 cleanroom, as illustrated in Figure 4, in which a robotic filling line is surrounded by a CVFS.

The closed-vial filling system offers a new containment concept, in which only closed containers are handled.

The advantage of the CVFS over the traditional isolator is its simplicity, in that it can be sanitized with classical sporicidal agents and does not require vapor hydrogen peroxide sanitization. The CVFS uses unidirectional, HEPA-filtered laminar airflow that exits through the bottom of the system, which helps maintain laminar flow and prevent turbulence. Isolators are still mandatory when the safety of the operator must be ensured (i.e., with highly potent drugs such as cytotoxics). Such isolators must be installed in an ISO9 cleanroom.

The advantage of the CVFS versus the Restricted Access Barrier System (RABS) is that in the CVFS, operator access is only possible via gloves, and the barrier environment is never compromised by door opening. Material entry is

limited to secured processes such as rapid transfer ports, airlocks, and e-beam irradiation units. With these limitations, an ISO8 clean room environment for the surroundings is sufficient to ensure the ISO5 quality inside the barrier.

Lyophilization with closed-vial technology

Closed-vial technology has also been developed for lyophilized products (8). Lyophilization is performed through the piercing trace, which is reopened inside the lyophilization chamber. After vial filling, a penetrator plate with multiple funnel shapes that fit on top of each vial is placed on a set of prearranged, bee-nest vials. As shown in figure 5, the vial/penetrator plate assembly is placed inside the lyophilization chambers and the shelves are moved down, thus pushing down the penetrator plate and reopening the piercing traces. The lyophilization cycle is launched while keeping the piercing trace open to allow evacuation of the sublimated water. At the end of the cycle, the shelves lift up and the natural elasticity of the stopper causes it to regain its initial shape and push the penetrator plate up. After exiting the lyophilization chamber, the vials are laser resealed and capped.

Closed vials can provide a safer solution for the patient and an easier solution for the pharmaceutical manufacturer.

The lyophilization cycle with closed vials is very similar to that of glass vials, except that the primary drying phase is longer. Tests show that closed-vial technology produces an improved cake surface, suggesting that the lyophilization process is more homogeneous. In the closed vial system, vials are more stable than in glass vial systems. The bee-nest assembly increases vial stability and the absence of contact between the shelves and the stoppers prevents stopper sticking. These factors reduce the risk of a vial falling down and knocking other vials on the shelf over.

Validation

Changes to the container design and process that occur when using closed-vial technology must be validated. To ensure that the technology is suitable for product approval, a series of tests that meet the required standards from Pharmacopeia and International Conference Harmonization (ICH) guidelines should be performed on the container materials, the properties and characteristics of the container closure, the processing technology, and the performance of media fill.

Conclusion

Closed-vial technology can provide a safer solution for the patient, in which the permanently closed container reduces the risk of external contamination, and an easier solution for the pharmaceutical manufacturer, in which ready-to-fill containers eliminate preparation steps. It can be used for any classical aseptic filling product. In addition, highly potent drugs (e.g., cytotoxics and immune-modulating drugs) and biohazard products (e.g., recombinant viruses) can benefit from the reduced breakage and spillage risks in the closed-vial technology. Other products that can benefit are lyophilized products, products that are susceptible to adhesion on glass, expensive drugs that can benefit from lower residual volume and lower breakage risk, and products with limited differentiation (e.g., generic drugs) in which the closed vial offers a solution to end-users. Closed-vial technology can also improve production capacity, and can be useful for setting up local filling from global bulk production. Some companies are investigating closed-vial technology in order to avoid issues with glass (e.g., delamination) (9).

Regulatory authorities appear to be open to innovations supported by a clear scientific rationale, as demonstrated by the acceptance of closed-vial technology for a pneumococcal vaccine by the European authorities in July 2011 (GSK Biologicals, Synflorix). A key driver for the approval was that the container is produced in an ISO8 environment but is kept permanently closed, which significantly reduces the risk of contaminant entry.

Acknowledgments

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