

# 15 | Genesis of the closed vial technology

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## INTRODUCTION

Aseptic processing requires “A strict design regime, not only on the process area, but on the interactions with surrounding areas and the movement of people, materials and equipment so as not to compromise the aseptic conditions” (1).

The Intact™ containers are closed and stay Intact™, from the point of assembly, through radiation sterilization and aseptic filling, and ultimately until delivery to the patient. As a result, the product, when needle filled through a proprietary re-sealable stopper, is never exposed to the environment from within the sterile formulation tank to the body of the patient. The “compliance” has been engineered by the Intact™ technology. Intact™ is aimed to overcome the Food and Drug Administration (FDA) concerns with aseptic processing:

... it is critical that containers be filled and sealed in an extremely high-quality environment. . . . glass containers have been subjected to dry heat; rubber closures to moist heat; and liquid dosage forms to filtration. . . each of these manufacturing processes requiring validation and control. Each process could introduce an error that ultimately could lead to the distribution of a contaminated product. . . (2).

The essential difficulties in traditional aseptic technologies are in the assembly processes that follow the sterilization steps for the individual components. Table 1 shows the human factors and risk involved in this process (3).

With the Intact™ technology, needle filling and sterile-closed containers, the container itself is the controlled environment and its own isolator, from sealing to filling.

Overall, the problem with aseptic technology is the high risks associated with open containers, exposed closures, and operator contact. These interventions will always mean an increase risk to the patient and because there is no truly safe intervention, the “perfect” intervention is one that does not happen (4).

## The Solution: Intact™ Technology

In the mid-1990s, closed systems were identified as superior to open systems in the aseptic processing of sterile active pharmaceutical ingredients (5). This Parenteral Drug Association (PDA) document was developed without mention of a risk assessment; nevertheless, it had a profound effect on Intact™ technology. Intact™ technology was conceived at Medical Instill Technologies, Inc., to address the need for a closed container that can behave as mobile isolator, keeping “Intact™” the inner surface sterile from sterilization through needle filling and laser resealing.

The materials used for the Intact™ container were specifically designed for compatibility with parenteral solutions and also to minimize the potential for particle generation during the penetration of the needle into the container (Fig. 1).

- *Plastic vial body*—Cyclic Olefin Copolymer (COC) medical grade, United States Pharmacopeia (USP) Class VI, high purity, high transparency, gamma sterilization resistant, best combination of low permeability coefficients. These are sourced from Ticona and Zeon. Many other medical-grade plastics have been used since.
- *Stopper*—Thermoplastic elastomer (TPE) of a special formulation, developed with a large polymer compounding company, meets USP class VI. Other non-TPE materials have since been developed.
- *Needle*—Specially designed and treated stainless steel for low friction forces during penetration/withdrawal, which combined with the special stopper limit the size and number of particles to much lower levels than with traditional vulcanized stoppers.
- *Intact filling machine*—The machine is extremely simple, only two key mobile parts, the vial conveyor and the rack of needles. No assembly occurs in the machine. As a consequence the

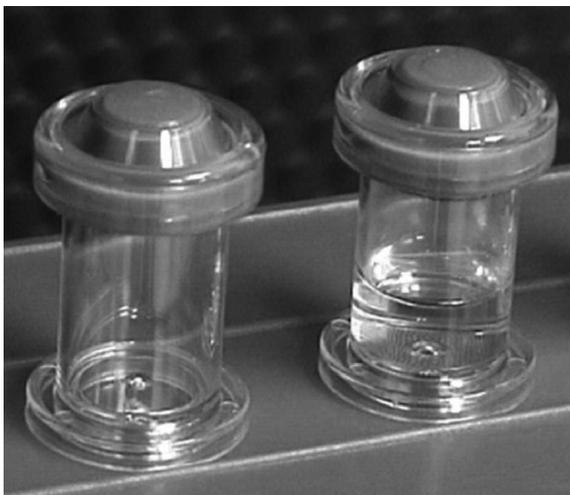
**Table 1** Aseptic Processing Risk Assessment: The Simplified Akers–Agalloco Method

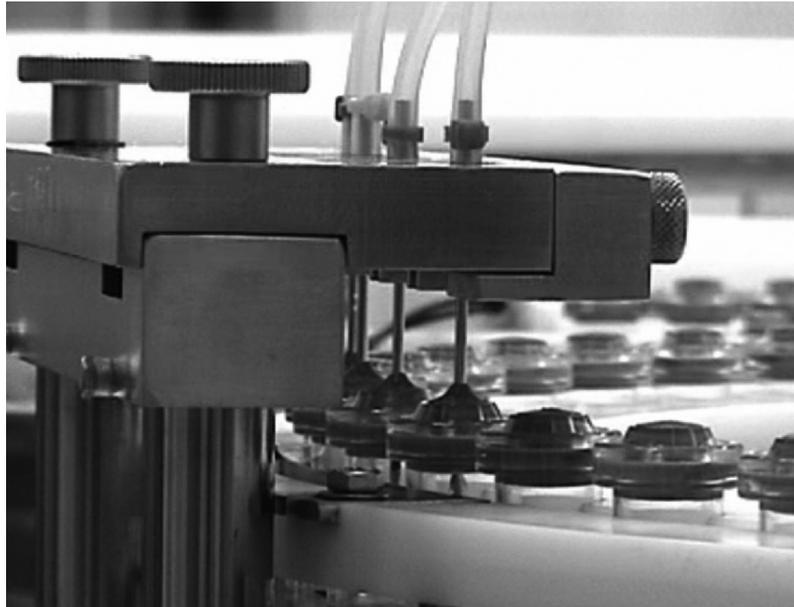
Task	Ease of validation	Personnel sensitivity	Associated risk
Sterilization	Easy	Low	Low
Room design	Not applicable	Not applicable	Moderate
Monitoring	Moderate	Variable	High
Sanitization	Difficult	High	High
Gowning	Difficult	Very high	Very high
Material transfer	Difficult	High	High
Aseptic technique	Difficult	Very high	Very high
Aseptic assembly	Difficult	Very high	Very high

downtime is significantly reduced. The product is never in contact with the environment, from the sterile formulation tank to the inside of the sterile vial. The vials can be needle pre-filled with nitrogen or other inert gas, with the same machine. Because the container is always sealed, the machine is nearly perfectly clean after operation, there are no splashing or broken containers, and CIP implementation is simplified.

The Intact™ filling technology was invented and developed in synergy with the stopper material of the closed containers. Noncoring needles, low-energy lasers for sealing the needle's path on the self-resealable stopper, special pigments to convert coherent radiation into heat enabling more efficient sealing, and IR sensors are used to assure that the melting temperature of the stopper material has been reached as a 100% quality control check. The Intact™ process offers several significant advantages over conventional aseptic filling that use glass containers, stoppers, and seals (Fig. 2).

- One supplier manufactures and assembles the complete container providing greater consistency and assured seal reliability.
- The assembly process is completed prior to sterilization essentially eliminating exposure during the process.
- The closure (the stopper itself) may be assembled and sealed within the molding machine and the closure integrity is 100% controlled, so that the inner surface of the closed intact vials/containers in general are never exposed to the environment (viables and nonviables).
- The sterilization process is performed on a sealed container eliminating potential for microbial ingress post-process.
- The inner surface of the closed vials are in contact with nothing but the liquid itself which is needle filled into the closed and sterile vials. Container product contact surfaces are never exposed even in the filling environment.

**Figure 1** Early-stage Intact™ container.



**Figure 2** Rotary Intact™ filler: Laser sealing station.

- The Intact™ self re-sealable septum is laser resealed within seconds after needle removal.
- The pin hole sealing process of the pierceable stopper is verified for each container.

A traditional aseptic performance validation of the first prototype Intact™ filler was completed at the PDA in August 2003 by way of three consecutive media fill runs at 10,000 Intact™ vials each (6). A summary of the runs are as follows:

- Intact™ vials were filled with sterile filtered soy-based nutrient.
- The two primary operators of the Intact™ filler had no previous aseptic processing experience and carried out all interventions.
- No advanced aseptic processing techniques or barriers were used (mere laminar flow hood).
- Three filling-needle changes were made and other nonroutine and high-risk manipulations were purposely conducted during the three tests.
- All filled Intact™ vials, totaling 31,500 units were incubated at 25°C for 7 days (molds and yeast) and 35°C for 7 days (aerobic bacteria) for a total of 14 days.
- Four hundred Intact™ vials were purposely filled and not laser resealed to characterize the safety factor of the self-resealing property of the stopper itself before laser resealing. These nonlaser resealed units remained sterile for more than 3 months until they were discarded.

Table 2 identifies the results of the media fills.

**Table 2** PDA-TRI Media Fill Results

Media fill run	1	2	3
Date	August 9, 2003	August 11, 2003	August 13, 2003
Units	10,377	10,730	10,645
Incubation	14 days		
# of Positives <sup>a</sup>	0	0	0
% Pass	100%	100%	100%
Microchallenge			

<sup>a</sup>Including the 400 nonlaser-resealed Intact™ vials.

A sample set of laser-resealed Intact™ vials were subjected to physical tests to assess the container integrity microbial ingress challenge and burst testing. The Intact™ vials were placed into a biobath of log7 concentration of *Brevundimonas diminuta* (ATCC# 19146) and successfully passed a 24-hour submersion and incubation. Finally, a USP <788> particulates test was performed on all Intact™ media fill vials with the following successful results (Table 3).

**Table 3** PDA-TRI Media Fill USP <788> Particulates Test Results

Particulate size	Limits	Test results/per vial
25 µm	600	3
10 µm	6000	31

The conclusion of the media fills performed identified that

- Closed vial filling systems proved robust where interventions and operator training represented worst-case operating conditions.
- Sterile preassembled containers significantly reduce the number of processing operations.
- A substantial reduction in system and process complexity was successfully demonstrated.
- Rapid system installation and validation.

To further advance the capabilities of the Intact™ filling process several enhancements have been made in newer fill systems to further improve upon the aseptic capabilities of the technology.

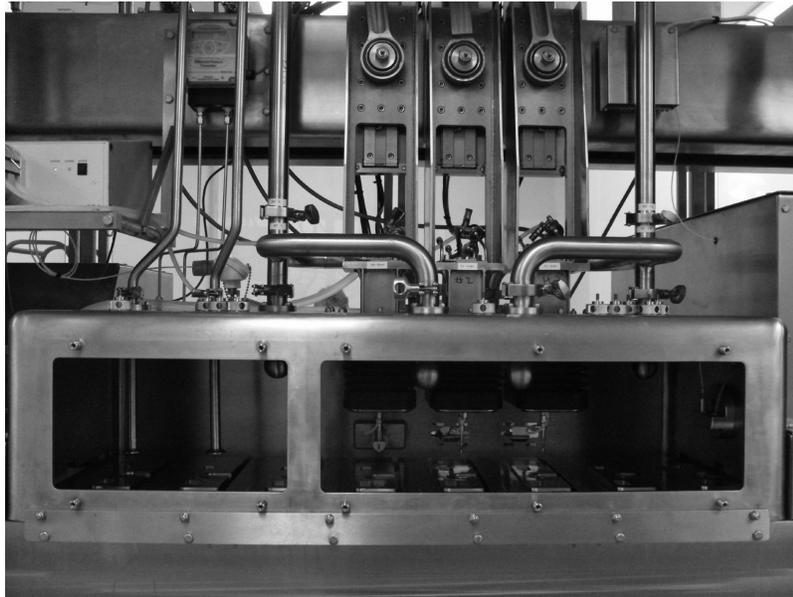
- The filling of Intact™ containers is performed in a hydrogen peroxide decontaminated isolator that operates without gloves. All internal movements are accomplished through mechanical or robotic systems. No human interventions are necessary during Intact™ filling.
- For extra safety precaution, the outer surface of the Intact™ container's septum are sterilized with hydrogen peroxide on-line upon entering the decontaminated aseptic fill zone. A characterization study for a log6 reduction of *Bacillus subtilis* spp. *niger* (ATCC 9732) was performed on a lot of 100 containers and determined to be met with minimal hydrogen peroxide concentration (7). This vapor hydrogen peroxide (VHP) station replaces advantageously any sterile transfer port.
- The integrity of each laser seal is supported by individual confirmation of temperature at the point of the seal (the laser melts the closure to reseal the opening).
- Linear filling platform replaces the first rotary platform.

These differences serve to enhance the reliability of the Intact™ filling relative to the risk of microbial contamination (Fig. 3).

In December 2003, an invitation from Dr. Peter Cooney and Dr. David Hussong of the Office of Pharmaceutical Sciences, CDER, FDA was given to Dr. Daniel Py to discuss the Intact™ technology based on the media fill performance at the PDA-TRI (Training and Research Institute) aseptic fill suite. Upon review of the data and discussion of the technology, Dr. Peter Cooney stated that "this is the paradigm shift in sterile filling technology" and praised the "engineered compliance" provided with Medical Instill Technologies.

#### ULTIMATE CHALLENGE TEST: MICROBIOLOGIC AEROSOL IN THE FILLER ITSELF

Although the risk for the closed vial to be contaminated is already essentially negligible as confirmed by multiple media fills under laminar flow, further experimentation has been undertaken in noncontrolled environments, to further determine the safety of the Intact™ filling process. One of the primary compliance expectations that are required with aseptic processing is continuous environmental monitoring to provide evidence that both viable and nonviable particulates have not breached the aseptic zone area. With Intact™ technology the risk of contamination is so low that several experiments were carried out to challenge both the closed vial and the Intact™ filler in a "dirty" environment worse than "filling in a parking lot," without



**Figure 3** Linear Intact™ filling (Universal Filler).

laminar flow or VHP on the stopper, as if the manipulator had forgotten the HEPA filters and the H<sub>2</sub>O<sub>2</sub> vapor on the stopper.

To create such a condition, a nebulizer, fan, and containment unit were used to place the filler and containers into a “dirty” environment. Both wet and dry aerosol microbial challenge tests were conducted with a log<sub>3</sub> concentration of *Bacillus subtilis spp. niger* (ATCC 9732). The goal was to determine if Intact™ filling with a closed container in a “dirty” environment without controls could allow the filling of a closed container with sterile tryptic soy broth. To further challenge the Intact™ technology, several units were filled and not laser re-sealed to further ensure the safety of the filling process. Figure 4 shows for the chamber and test system with a clinical Intact™ filler used during testing.

Before running the nebulizer with either a dry or wet microbial aerosol, two negative controls were filled via Intact™ filling without environmental control. Additional environmental monitoring to confirm the level of microbial aerosol was conducted throughout the run. After the test samples were run, a 30 to 300 CFU/mL of *Bacillus subtilis spp. niger* (ATCC 9372) was added to two closed containers to establish positive controls. After 20 closed containers were Intact™ filled in a dry aerosol (concentration of  $1.3 \times 10^3$  CFU/1000 m<sup>3</sup>) and 10 closed containers were filled in a wet aerosol (concentration of  $4.2 \times 10^{10}$  CFU/1000 m<sup>3</sup>) the samples were incubated for 14 days at 30°C with evidence of no growth (8). Further evaluations at increased *Bacillus subtilis spp. niger* (ATCC 9372) concentrations are under way to establish an edge of failure value. With this information larger sample size studies at this log<sub>3</sub> concentration will be established.

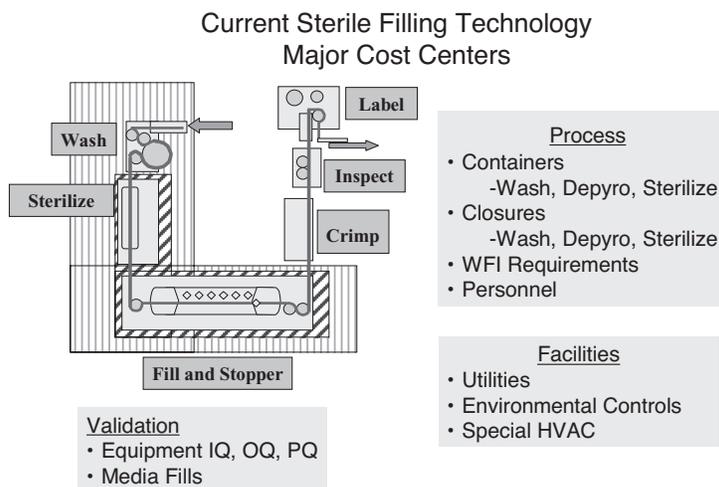
### Process Benefits

An additional advantage beyond the added compliance using intact™ filling is attained by reductions in both labor and time. The Intact™ process eliminates the extended exposure of sterile/depyrogenated containers and closures to the operating environment. Intact™ containers are supplied sterile and sealed, such that contamination ingress is eliminated. In addition, concerns for sterilization of product contact surfaces for the closure system at the fill site are also eliminated. The only concerns with the Intact™ process are the sterility of the closure surface at the point of penetration, the integrity of the re-sealed container, and maintaining sterility of the fill needles over the duration of the filling process.

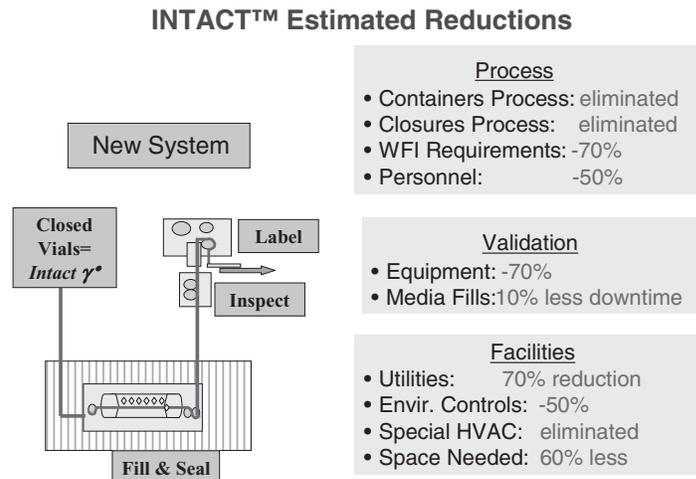


**Figure 4** Aerosol microbial challenge testing chamber unit

Moreover, the Intact™ filling eliminates several of the major cost areas associated with filling of glass containers by aseptic processing regardless of the specific technology: conventional, RABS, or isolator-used. Water for injection requirements are dramatically reduced as the only requirement for water is that required in the formulation. Washing of stoppers and glass containers prior to sterilization is eliminated as well. Sterilization of stoppers and fill parts by steam are eliminated as well as depyrogenation by heat of the glass containers. The expense of the equipment and the utility costs to operate these systems is thus averted as well. Figures 5 and 6 shows a cost comparison of current aseptic technology and Intact™ technology (9).



**Figure 5** Operational cost for current aseptic technology.



**Figure 6** Operational cost for INTACT™ technology.

All the traditional operations and controls for sterile washing, sterile drying, sterile transfers, and as a result, are obsolete due to the “engineered compliance” resulting from transfers and filling of the Intact™ closed vials. The estimated saving on the operation cost is about 65% and this does not take into account the dramatic improvement of the downtime, and of the consecutive elimination of the numerous media fills and quarantines usually needed with aseptic filling of the traditional open vials.

### APPLICATIONS OF THE INTACT™ FILLING TECHNOLOGY TO NONPRESERVED PRODUCTS

The Intact™ vial for a nonpreserved vaccine was the first application of the Intact™ filling technology. In 2004, Intact™ filling and Intact™ “Diablo” vials were licensed by Medical Instill Technologies, Inc., to GSK and Aseptic Technologies (a subsidiary of GlaxoSmithKline) for filling nonpreserved vaccines and nonpreserved injectables (chapter 40 of this book outlines the related capabilities and experience of Aseptic Technologies, the GSK-owned company to which we licensed the Intact™ vials and filling technology mentioned above for vaccines and pharmaceutical injectables and that they now make available for commercialization in that field of use under the “Crystal™” brand).

Infant bottle (with teat) nonpreserved infant formula was the second application of the Intact™ filling technology. In 2005, Medical Instill Technologies, Inc., invented and developed an infant bottle to be Intact™ filled, and licensed it to a leader in the nutrition field for an unmatched safety level provided with infant formula. A focus of this application is premature infants who have yet to develop their immune system. In addition to the Intact™ baby bottle for single use, an Intact™ multiple-dose noncontamination bulk dispensing package for infant formula also was licensed to the same leading nutrition company for use in ambient conditions. This technology expands to allow for the use of sterile dispensing (Intact™ valve) from first to last dose in nonrefrigerated conditions for over a month of sterile use.

### The PureDose® Valve

The application of the Intact™ valve evolved into the PureDose™ valve for dispensing solutions, suspensions, gels, and creams in pharmaceutical and medical device applications. The PureDose™ valve is a one-way viscoelastic valve that performs as a mechanical barrier to bacterial ingress, over multiple doses. This concept allows for the elimination of preservatives, now shown to be associated with numerous topical and systemic side effects. In addition, this allows for an increase in stability through the prevention of oxidation and no microbial ingress. The

viscoelastic valve was designed based on a coronary artery that is itself a pump, using stress differential to eject residual volume. It can be described as the valve behaving by “squeezing a cherry pit” or product from the container to prevent any microbial ingress.

A line of containers for various topical and systemic administrations are in the development process. Approximately 600,000 microbiological challenge tests have been successfully carried out with the PureDose™ valve.

### Next-Generation Intact Products

Further applications of Intact™ technology with the PureDose valve™ have led to new concepts in the areas of sterile powder filling, sterile connectors, lyophilization processing, and a second generation of Intact™ vials for multiple dosing. Modifications to the container and filler can accommodate both lyophilization and dry powder filling.

**The sterile connector** allows for the immunocompromised patient, either at home or a hospital, to prevent contamination of viable particulates into their bodies when either feeding or receiving pharmaceuticals.

**A needleless transfer container** has also been developed to sterile transfer any liquid product into another sterile closed container. The first application is the transfer of a complementary nutrition product into another nutrition product container. The same container will then be used for sterile transfer of pharmaceuticals without a needle.

**A sterile powder filling machine** using the Intact™ technology will be available for filling closed vials with sterile powder milk before the year end. The same system will be usable for sterile filling pharmaceutical powders. There are two main advantages of such a system:

- The absence of powder projection in the filling machine, and as a consequence, a very low-maintenance filler is provided;
- It allows for reconstitution of the product with sterile water through the needleless transfer feature into another closed sterile container.

This new series of Intact™ devices is aimed at preventing any contact with a nonsterile environment during the reconstitution of the product, during the needleless transfer, and/or multiple dose delivery. As a consequence, Intact™ devices will significantly contribute to the reduction of nosocomial infections and associated costs.

### CONCLUSION

The Intact™ filling and noncontamination valve technologies, validated in vaccines and nutrition products, has generated a “paradigm shift” to reach the epitome of sterile filling through the elimination of the multiple interventions that had previously made aseptic filling operations increasingly complex. As a consequence, with the Intact™ technology, the increasingly complex compliance has been “purely” engineered as Dr. David Hussong of FDA has said. The elimination of the open container and of the separate stopper reduces the contamination potential to levels believed unattainable by other means.

It is also a stepping stone for filling and reconstitution of powder products and a variety of noncontamination multidose delivery devices. The Dr. Py Institute is the technology leader in developing these sterile filling and nonpreserved dispensing devices. The Intact™ technology prevents contact between the products and the environment from within the sterile formulation tank to the bodies of the patients. The scope of this technology has been proven in medical devices, pharmaceutical, nutritional, and skin care products. It has been proven to also reduce manufacturing cost and to simplify operations, especially for emergency supply in much less controlled environments. It is now aimed at reducing significantly the incidence nosocomial infections.

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# 40 | Innovation in aseptic processing: case study through the development of a new technology

Benoît Verjans

## INTRODUCTION

As many drugs can be administered only through systemic way, due either to patient condition or due to bioavailability of the drug itself, the continued availability of existing drugs and development of new parenteral formulations remain a must in the pharmaceutical industry. Among parenterals, aseptically filled drugs are more and more common, especially since many of the new biological drugs cannot resist terminal sterilization.

Four major issues can be pointed out, being related to injectable drugs in general or to aseptically filled drugs in particular.

The first issue is patient safety. In contrast to terminal sterilization, aseptic processing does not guarantee a complete absence of bacterial presence and, thus its potential, proliferation inside a liquid solution. In case of such contamination, patient life is at risk as it can face septic shock and death. The presence of operators in the vast majority of aseptic processes means that the greatest source of potential microbial is ever present.

The second issue raised more specifically for vaccines is that the presence of preservatives, such as thimerosal in vaccines, has been challenged by various governmental organizations such as the Food and Drug Administration (FDA), the Center for Disease Control (CDC), and the National Institute for Health (NIH) in the early 2000s (1). As a result, vaccines manufacturers took the decision to withdraw preservatives from vaccines, eliminating the last safety barrier in case of presence of single bacteria.

The third issue is counterfeiting, a new threat, which has started to rise and in particular to target injectable products. The main driver to sell counterfeited injectable is that huge benefits can be achieved on selling high price vials. Several counterfeit batches of expensive biologics have already been identified and withdrawn by the FDA. Counterfeiting is a major issue on various points of view:

- Economic point of view: It is estimated that about 10% of worldwide drugs are counterfeited, generating a revenue loss of more than 32 billion USD. Counterfeiting is so severe that it can reach up to 50% of drugs sold in some countries such as Nigeria (2).
- Patient quality point of view: The quality of counterfeited drugs is seriously impaired. In some cases, the active ingredient is not present or not at the right dosage, leading to the lack of treatment and worsening of condition. For example, 2500 people died in Nigeria from meningitis among 25,000 people being vaccinated with a counterfeited vaccine without antigen inside. This patient risk is not specific to the third world countries and happens in developed countries such as the United States. The most well-known case is the contamination of Tim Fagan, a recent transplanted teenager who has been contaminated by a poor quality copy of the Amgen's drug Epogen. As a result, a law, named Tim Fagan's law, has been approved and has reinforced the legal actions against counterfeiting companies and people.

In parallel to counterfeiting, bioterrorism became a real issue since September 11, 2001 when people realized that terrorist can develop multiple ways to attack Western countries.<sup>1</sup>

The fourth driver was based on experience with glass vial filling in an isolator. The equipment used has reached such a level of complexity that each produced batch requires not only high resources in qualified human resources for operation and maintenance but also in quality assurance/quality control support. The complexity is driven by the washing, siliconization

<sup>1</sup> Glass vials, being very easy to copy, are good candidates to carry viruses and other biological weapons.

and sterilization of vials and stoppers, the high-speed filling/stoppering, and the high-speed aluminum capping. As a result, both operating expenses and investment for equipment, large utility production units, and building space have exploded. For example, a filling line under isolator with a nominal capacity of 42,000 vials/hr needs approximately 300 m<sup>2</sup> of class C (or class ISO 8) clean room, and overall equipment price would exceed 10 MM EUR.

These four issues triggered GSK Biologicals to investigate a new technology for aseptic filling of injectable drugs and created Aseptic Technologies to address this objective. After analysis of these issues, Aseptic Technologies determined that it was possible to create a new technology that would be able to address all these issues. This means that the technology should

- Provide a top-class sterility assurance level during operation
- Provide a reinforced security against counterfeiting and bioterrorism
- Simplify aseptic filling processes and operations.

### THE CLOSED VIAL CONCEPT

The solution identified to address the three points described above is the Crystal<sup>®</sup> or Closed Vial technology (3,4). The concept is based on a closed container that can be filled through a heat resealable stopper (initial technology licensed from Medinstill Inc.) and, to simplify the process, a presterilized container is provided stoppered and ready-to-fill.

The vial is made of cyclo olefin copolymer (COC) whereas the stopper is made of thermo-plastic elastomer. The latter is mandatory to allow heat resealing. For example, classic rubber stopper would burn under heat source but not reseal.

The vial manufacturing consists in three major steps:

- The two main elements of the vial are molded in class 100/ISO 5 to ensure the cleanness of the inside of the vial. They are molded at the same time and robots perform assembly of the two elements. Thanks to the specific shape of the stopper adapted to the vial body, the assembly strength is sufficient to hold them together. Thanks to rapid closing, the air entrapped inside the vial is from class 100/ISO 5 environment.
- The second step consists in the addition of top and bottom rings to secure closure integrity. This is completed on a rotary table with tight visual control of presence and positioning of each element to ensure rejection of any vials with missing or misplaced part. The vials are then packed in polypropylene akylux boxes and double wrapped in polyethylene bags. This packaging is the packaging used for loading the vials on the filling line (see below).
- The third step is the sterilization of the closed vial. As there is no glass, gamma-irradiation at minimum 25 kGray is entirely appropriate to ensure that the vial is sterile without altering its color. At the end of those three steps, the vial is clean and sterile and therefore ready-to-fill once delivered to the pharmaceutical manufacturing site.

The vial filling process consists in five major steps:

- The loading is performed on tables equipped with long arms to perform box opening and vial loading on accumulation table. By keeping the operator away from the vial, risk of contamination of the outside of the vial is minimized.
- Nevertheless, as it is not possible to exclude an operator mistake resulting in a contamination on the stopper, the vial can be processed through an e-beam to resterilize the stopper surface. Effectively, this surface is the most critical one because it will be penetrated by the needle during the piercing process (see next step). The e-beam delivers a dose of 25 kGray of beta irradiation on the stopper. This dose is sufficient to resterilize the surface, but penetrate not in depth in the material (irradiation dose is maintained to a depth of 30 μm and then starts to decrease rapidly).
- The vial is then filled with a pencil point needle that has been designed to
  - Minimize particle generation during piercing
  - Avoid coring of the stopper leading to large particles and absence of material necessary for optimal laser resealing
  - Dispense smoothly the liquid with a 30° angle, thanks to lateral holes
  - Eliminate overpressure due to liquid filling in a closed container, thanks to ventilation slots located on the needle sides at the height of the stopper.

- After filling, the vial is immediately resealed by a focused laser beam. The laser system has multiple functionalities to ensure optimal resealing of the piercing trace:
  - A flat-top curve lens that provides an equal distribution of the energy on the entire area hit by the laser to avoid both burn spots and low energy spots.
  - A feedback system that detects the presence and the intensity of the laser shot. This system is a Process Analytical Technology (PAT) to perform 100% check of the quality of the resealing.
- The final step is the capping of the vial. Thanks to plastic molding, the capping is made by snap fitting of polyethylene caps. A simple pressure is sufficient to ensure capping. The cap has the unique ability to ensure additional closure integrity at the level of the stopper surface. This closure integrity is achieved, thanks to a rib located on the inner face of the cap and that is pressing on the stopper. Therefore, the stopper surface is kept in the same class environment as the one around the capping station; and maintained until used by the medical practitioner.

An additional step can be added to address counterfeiting as a specific marking with either radio frequency identification (RFID) chip or laser marking. The RFID can be placed simply during capping. It can be easily located on the inner face of the cap and therefore be entrapped between the cap and the vial during capping. A simple coding station can be located before exiting the filling line. As a result, a secured RFID is coded before any operator could touch the vial.

The laser marking process has been designed on the same concept of having a coded vial coming out of the line. The marking can be made on the top ring lateral side that offers a surface big enough to perform either alpha-numeric coding or 2D matrix coding, again, before the vial exits the filling line.

Obviously, the Closed Vial technology introduces both new filling technologies and a new container. Therefore, to ensure that the technology is suitable for injectable drugs, it has been fully studied and validated to ensure that it meets all requirements from authorities regarding approval of container and filling process. Both the European and US Pharmacopeia provide mandatory detailed tests for polymeric materials such as material characterization, acceptable level of endotoxins and particle, and closure integrity tests. All of these tests have been performed successfully and, in addition, detailed extractable and leachable studies have been conducted to assess in depth the materials in contact with the injectable drug.

The final proof of robustness was the performance of a media fill inside a nonclassified environment. To that end, two prototype lines located in a workshop have been used to fill over 25,000 closed vials with media and none has been contaminated. Overall, over 100,000 vials have been filled without contamination.

#### **ENVIRONMENT REQUIRED DURING THE VARIOUS MANUFACTURING STEPS**

On one hand, to ensure that the Closed Vial technology meets the latest requirements from authorities regarding aseptic drug production, a high-quality environment must be continuously provided during all steps of production. On the other hand, the Closed Vial technology ensures by itself a better safety for the patient (e.g., the container is permanently closed during all filling operation). Therefore, through the use of quality by design this technology allows for the simplification of many processes, including the environment during both vial manufacturing process and vial filling process.

#### **Environment During Vial Manufacturing**

The cleanliness of the inside of the vial is a major concern, as it is closed before use and there is no opportunity to withdraw particles and endotoxins after container closing. Sterility is not an immediate concern at that time as the gamma sterilization will penetrate thoroughly all parts of the vial, but bioburden should be also minimized to avoid endotoxin generation. To ensure that cleanliness, the vials are molded in class 100/Grade A/ISO 5 environment. Operator presence during operation is strictly forbidden and environmental monitoring is permanent. Inside the room, the only equipment present are the molds, the robots to pick and assemble both vial parts,



**Figure 1** Illustration of the clean room class 100/Grade A/ISO 5 used for vial body and stopper molding, followed by robot assembly.

and a vibrating rail that deliver vials outside this room once closed (Fig. 1). Special care has been put on the design of the room.

- The concept of molding machine is designed with a mold and mold plates in an overhang “cantilever” position. Only the mold, the supporting platens, and the tie bars are located inside the clean room whereas the rest of the machine is outside. As the mold is opening, clean air can flush through the open space, with no underlying machine frame or component disturbing the flow. Special care is devoted to details, like cooling water hoses and electrical connections located under the mold.
- The molds are operating without addition of any additive to facilitate exit of parts. These additives are considered as a source of contaminants such as leachables and particles.
- The robot hands have been designed to touch only the noncritical surfaces of the vial parts. All robot surfaces are easily cleaned and grippers (difficult to clean) have been avoided. The component holding is done by cavities in the flat hand front surface, with vacuum in the center of this cavity.
- The selected robots are suitable for operation in high classification clean rooms, as usual in the semiconductor industry (class 10/ISO 4).

After molding and assembly of the two parts, they are transferred to a class 10,000/ISO 7 environment suitable for further automatic assembly and packaging. It is critical that the inside of the vial is not exposed to this room. Therefore, the assembled vial body–stopper is inspected with camera to ensure that the stopper is properly in place. Any unit with a missing stopper or partially lifted stopper is discarded. The vial handling systems have been designed to avoid risk of marks and scratches on the highly transparent body surfaces, allowing a free view for inspection for particles after filling. High tech CMM (Coordinate Measurement Machine) are also used to periodically evaluate all critical dimensions.

The result of the above practices is a vial where visible particles are totally absent; the level of subvisible particles is extremely low and difficult to measure. Also bioburden has been found to be zero on all tested samples.

### Environment During Vial Filling

At this step, the vial remains permanently closed and therefore the risk of contamination due to the presence of bacteria in the environment is very low. As shown in Figure 2, when the needle is piercing the vial, the stopper remains tight on the needle surface. This effect has a wiping effect keeping potential contaminant out of the vial. The biggest risk is located at the level of the holes dispensing the liquid. This concept of the vial staying closed at all times means that the vial can be considered as “an isolator at item level.”

The environment around the filling area is provided with an isolation system: the CVFS (Closed Vial Filling System). In this chapter, the main characteristics of this system are described.



**Figure 2** Piercing of the vial showing the tight contact between stopper and needle.

The CVFS is defined as: “An aseptic filling system providing an environment achieving uncompromised Class 100/Grade A/ISO 5 protection that surrounds containers which are delivered closed and sterile inside, are filled through their stoppers and then immediately re-sealed to preclude the possibility of microbial ingress.”

The key characteristics of a CVFS have been defined using a “quality by design” process and can be summarized as:

- *Surrounding environment:* Surrounding room classification should be class 100,000/Grade C/ISO 8 minimum in operation.
- *Enclosure system:* Operators must be separated from aseptic processing operations by rigid walls to ensure complete physical separation. No door opening is allowed during operations and is allowed only after line clearance. To prevent unintentional opening, the doors are interlocked and linked to alarm systems. In case of door opening, all materials still present inside the CVFS (empty vials, filled vials, bulk in fluid path, caps, etc.) are discarded. The rigid wall is equipped with glove ports and rapid transfer ports (RTP) to allow manual intervention and component transfer such as needle, solution, or caps. The ceiling is equipped with HEPA filters to supply continuously unidirectional airflow from the ceiling of the enclosure. The environmental control system operates primarily on the principle of aerodynamic separation (air overspill) as defined in ISO 14644-7. An open bottom with air exit inside the surrounding environment is appropriate for classical products. For highly potent and/or toxic products, a closed bottom is recommended to maintain operator protection.
- *Entry of closed and sterile containers:* The vials can be entered either through closed systems such as beta-bags connected to RTP or polyethylene bags treated in a vapor hydrogen peroxide (VHP) airlock. These systems are adapted for small quantities of vials due to productivity limitations. For high-speed lines, a manual opening can be performed. As the line can be installed in a class 100,000/Grade C/ISO 8 and the design cannot exclude unintentional contamination of the stopper surface; surface sterilization is mandatory before entering the CVFS. This can be achieved with an e-beam as described above.
- *Sanitization and environment quality in the enclosure system:* “High-level disinfection” of all nonproduct contact surfaces is achieved with an appropriate sporicidal agent before batch manufacture. All the product contact surfaces, such as fluid path, are sterilized in an autoclave and entered through RTP.

### KEY ADVANTAGES OF THE CLOSED VIAL TECHNOLOGY OVER THE CLASSICAL GLASS VIAL TECHNOLOGY

As a reminder, Aseptic Technologies was interested to improve the aseptic filling on three major axes:

- Offer a better solution to the patient to reduce risk of contamination that demand being exacerbated by the withdrawal of preservatives
- Improve supply chain to reduce counterfeiting and bioterrorism risks
- Leverage a solution that is less complicated and less expensive compared with current glass vial technology.

The expectations placed on the Closed Vial technology can be summarized in two words: safer and easier. This chapter details how the technology can be proved to provide a better solution compared with glass vial.

#### Safer

The Closed Vial concept is the essence of reduction of patient risk due to contamination, as the inside of the sterile vial is never exposed to the environment. Thus, it is impossible for a contaminant to penetrate and proliferate inside the container in contact with the liquid product. With the glass vial technology, vials can be exposed for up to 20 to 30 minutes after depyrogenization, from exit of the hot air tunnel up to stoppering station. This exposure could lead to ingress of living organisms that can be present inside the manned environment. The situation with stoppers is even worse as stoppers are often loaded for a full batch, which means that stopper surface can be exposed several hours. These risks have been minimized by increased usage of systems such as isolators and restricted access barrier systems (RABS) but such systems do not guarantee a 100% protection of the product against contamination.

With respect to the fill needle, it is impossible to avoid exposure to the environment, but the Closed Vial technology offers an additional safety point which is the wiping of the needle by the very flexible material of the stopper. Moreover, the design of the equipment has taken into account the most critical current good manufacturing practices (cGMP) requirements. In particular, care has been taken to avoid as much as possible the presence of equipment above the needle to minimize airflow pattern turbulences.

Particle studies have shown that the entire process (including vial manufacturing, piercing, laser resealing, and 23-gauge needle piercing to collect the liquid) generates half the amount of particles with the closed vial compared with glass vial. This particle reduction is obtained thanks to a production process that is made in a class 100/ISO 5 environment and by using noncoring needle to pierce the vial. The use of molded plastic materials allows the introduction of new features to improve closure integrity (right angle snap fit assembly) or to facilitate particle inspection (elevated bottom), all contributing in attaining top-level quality for the product. In addition, the use of plastic cap provides additional closure integrity at the level of the stopper surface. The protection of the piercing trace is an important health issue, as cleaning of stopper is frequently inadequately performed by health care professionals. This can range from absence of cleaning or light wiping that is not sufficient to eliminate bacteria. Local infections have been often shown due to needle contamination when the product is collected from the vial.

Regarding supply chain, a safer solution is achieved through both secure coding and shock resistance (the plastic vials are less susceptible to breakage as compared with glass).

#### Easier

The Closed Vial technology substantially simplifies the aseptic filling process for the pharmaceutical manufacturers. In particular, the key simplifications are the elimination of the preparation steps mandatory for glass vials and rubber stopper. These steps include washing, siliconization, and sterilization. Other simplification are the elimination of the high-speed stoppering under aseptic conditions, the replacement of the aluminum cap crimping by snap fit of plastic cap, and the use of the CVFS in place of isolator.

As a result of the simplifications, the validation requirements are also reduced. In particular, validation efforts required for water for injection used for vial body and stopper washing can be eliminated. The new technologies introduced, that is, e-beam sterilization and laser

resealing are relatively easy to validate and are performed for each batch. All these simplification have been shown to reduce the total cost of operation, thanks to reduction in operating expenses (fewer operators are needed, less validation work should be performed, only limited electricity and no water for injection is needed, etc.), a better productivity (less residual volume, less vial breakage, etc.), and a reduction of investment (smaller clean room, less expensive equipment, etc.).

The technology also proved to be easier for health care professionals. A market study conducted with 246 professionals in hospitals (doctors, nurses, and hospital pharmacists, both in Europe and United States) has shown that 87% of them expressed a preference for the closed vial versus 7% for the glass vial. The main reasons pointed out are the ease to vial handling, vial opening, stopper piercing, and liquid collection. Other sources of preference were an unbreakable vial and a better asepsis for the patient (especially the protection of the piercing area).

In conclusion, the Closed Vial technology has not only proved itself as a suitable technology for the aseptic filling of injectable drugs but also provides a series of advantages to answer the most recent challenges faced by this industry.

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