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2017

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VACCINE DEVELOPMENT AND MANUFACTURING 2017

UBM

Moving to Closed Systems for Aseptic Processing

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Alternatives to time-consuming, error-prone operations promise to reduce vaccine manufacturing costs and improve facility flexibility.

Aseptic processing continues to challenge vaccine manufacturers. The operation, which involves filling a container with vaccine, and then sealing the container in a pristine environment, requires highly trained personnel and entails substantial costs, both for infrastructure and for everyday operation. The formulation, container, closure, and processing equipment used for aseptic processing must be sterilized individually, and substantial precautions taken to maintain their sterility throughout filling and sealing operations (see **Figure 1A**). As FDA explains in its aseptic processing guidance (1), the overall process involves more variables than terminal sterilization, and each step requires validation and control.

As the guidance states, "Each process could introduce an error that ultimately could lead to the distribution of a contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control."

Operators have long been identified as the predominant source of microbial contamination in aseptic processing (2). In fact, the very term "aseptic processing" represents a compromise, acknowledging that truly sterile process conditions remain unattainable, given the people and equipment required, and their potential to contaminate product. Best aseptic processing practices can at least ensure that the environment is free of pathogenic microorganisms that might put patients at risk if they wound up in the product.

Unfortunately, instances of contamination continue to occur, and regulators have penalized a number of vaccine manufacturers for failure to maintain a truly aseptic environment in filling and other

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operations. At times, these issues have led to shortages of crucial vaccines. At the same time, aseptic processing contributes to the complexity and high infrastructural and operating cost of vaccine manufacturing (3), at a time when prices and profitability for vaccines have remained depressed (4)

If aseptic processing is to continue to improve, compliance will have to be engineered into equipment design. Simpler, more elegant designs will be required.

This article will look at aseptic processing and the development of closed systems designed to prevent operators from coming in contact with the process, and will outline the evolution of one closed system technology for aseptic processing, describing how it works and summarizing results that have been seen in media fills performed both at the developer's facilities as well as those of its licensing partner.

Central to closed system performance for aseptic processing is the means to connect one closed system to another without contamination ingress. While closed systems have been used in pharmaceutical and biotechnology for some time, they have typically used a limited number of connections between their separate components. The closed system described in this article provides a means for closed system transfer from a closed filling system to pre-sterilized closed containers without exposing the product to environmental conditions and potential contamination.

Eliminating human contact with the product

Over the past few decades, aseptic processing performance has improved substantially. However, manufacturers still face significant difficulties, especially in aseptic processing lines in older facilities (5). Most advances have focused on the singular goal of separating operators from the process, or eliminating excessive or direct operator contact with sterile materials (6).

Many of these improvements have centered around the use of isolators or Restricted Access Barrier Systems (RABS). Concurrently, global regulators have mandated extensive environmental and procedural controls in attempts to increase the safety level in aseptic processing. These extensive controls are described, in exhaustive detail, in 21 *Code of Federal Regulations* (CFR) 211, FDA's 2004 Aseptic Processing guidance and EU *Eudralex* Annex 1 (1,7,8) .

Nevertheless, concerns about the safety of aseptically manufactured sterile products persist. If aseptic processing is to continue to improve, compliance will have to be engineered into equipment design. Simpler, more elegant designs will be required than the past decade's state-of-the-art, in order to ensure the safest products possible. Building compliance into equipment will be especially critical in emerging markets where the infrastructure and trained, skilled workforce required for reliable aseptic processing are often lacking.

Closed systems have become the Holy Grail of aseptic process development. The Parenteral Drug Association (PDA) defines them as systems that are or can be (9):

- Sterilized while closed prior to use
- Pressure and/or vacuum tight
- Used without breaching system integrity
- Adapted for fluid transfers in and/or out while maintaining asepsis

Figure 1A, 1B, 1C: Open containers/open needle; closed container/open needle; and closed container/closed needle configurations.

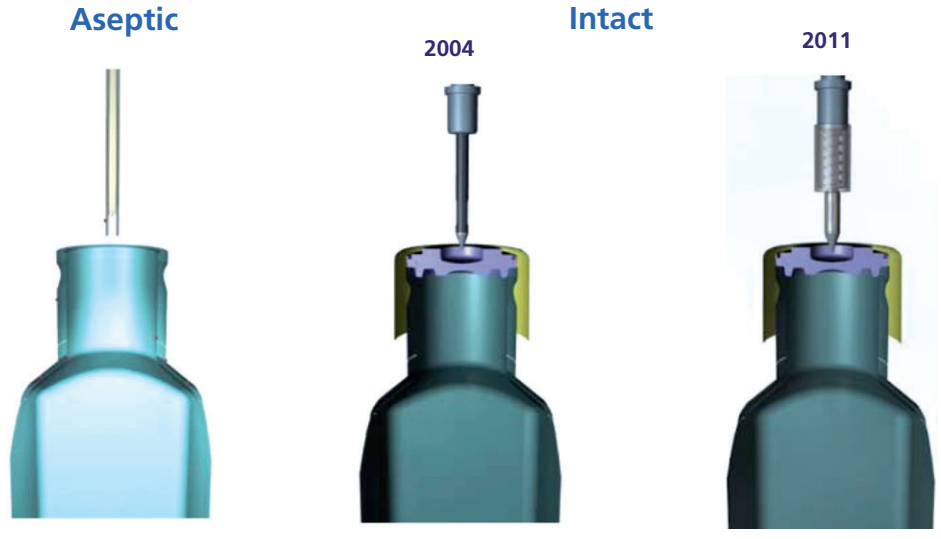

Table I: Medinstill 2003 media fills.

Open needle / Closed vial	Background environment	Fill environment	Media	Media fill results	
				# Units tested	# Units contaminated
2-ml vial,	Grade B	Grade A	TSB	31,752	0

- Connected to other closed systems while maintaining integrity of all closed systems
- Used with sterilizing filters that are integrity tested and traceable to each product lot.

The move to closed systems

A number of companies are working toward this goal, taking different approaches to separate operators from product. One approach taken by the Canadian manufacturer VanRx, works from the outside in. Based on best practices in the semiconductor industry, the platform uses robots to fill nested syringes, vials, and cartridges automatically in enclosed gloveless isolators, which shield the entire process and product from any exposure to outside contaminants (10).

Working from the inside out are processes that were developed by MedInstill Technologies (MedInstill). In 2003 and 2004, the company first successfully demonstrated an aseptic filling technology in which the closure on a sterile closed vial was penetrated by a non-coring needle and the opening in the container then re-sealed by using a laser to re-melt the closure (see **Figure 1B**) (11). This technology eliminates the need for operators to prepare and aseptically handle both container and closure (see **Table I** for a summary of media-fill test results of this initial technology.) Tests were conducted in an ISO Level-5 cleanroom at the PDA Training and Research facility.

The use of an open-eye filling needle mandated that the environmental controls associated with traditional aseptic processing be maintained in the background environment as well as over the filling needles. Aseptic Technologies (originally a GSK subsidiary, now owned by Skan AG) licensed the technology, and one product filled with this closed-vial technology has already been approved

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Table II: Aseptic Technologies' media fills.

Open needle / Closed containers	Background environment	Fill environment	Media	Media fill results	
				# Units tested	# Units contaminated
Various	ISO 8	Grade A	Various	74,538	0
Various	ISO 5	Grade A	Various	14,100	0

Table III: Medinstill 2011 media fills.

Open needle / Closed vial	Background environment	Fill environment	Media	Media fill results	
				# Units tested	# Units contaminated
250-ml. bottle	>1 x 10^2 CFU/m^3	>1 x 10^2 CFU/m^3	TSB	4,000	0

for use, while others are awaiting approval by FDA and EMA (12).

Over the next nine years, Aseptic Technologies ran a substantial number of media-fill tests to support their filling technologies and client container requirements (see **Table II**).

Meanwhile, designers at Medinstill sought a way to develop a sterile transfer system for filling closed containers, one that would prevent exposure of the sterile drug and product contact surfaces to surrounding non-classified environments and contact with operators within that environment.

With this goal in mind, media fills were performed using different variations of the closed vial technology, in background environments that ranged from ISO Level 7 to unclassified (see **Table III**). The filling enclosure was supplied with high-efficiency particulate (HEPA)-filtered air, but filters were switched off in some runs, which were designed to simulate worst-case conditions that might exist in some processing environments.

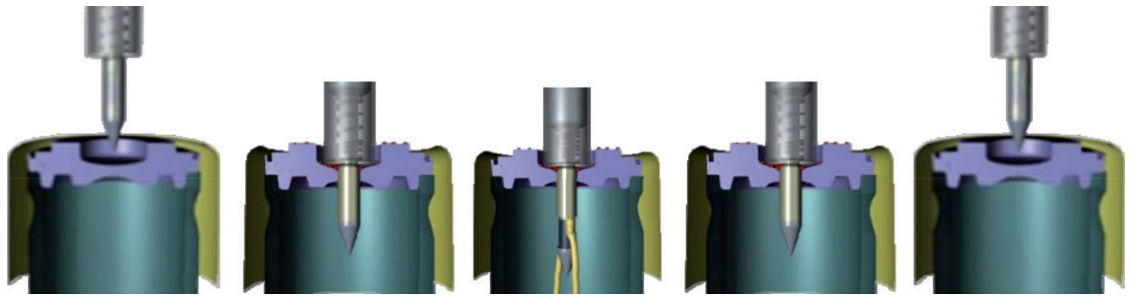
Development aimed to eliminate the need for environment control to protect sterilized product, fill components, and filling parts so that the resulting process would exceed the capabilities of the best existing separative designs. Equipment such as RABS or isolators still rely on environmental controls to protect exposed product containers, elastomeric closures, and filling heads. The basic goal of this work was to create a reliable means for truly closed sterile transfer in aseptic processing that would not rely on environmental controls of any type.

Closing off the fluid pathway

Ultimately, the designers applied closed system considerations, not only to the container but to the entire fluid pathway at all critical points in the process (see **Figure 1C**), at the point of fill, and where the filling system connects to the outlet of the sterilizing filter. The result was ISCON (short for Intact self-closing-opening needle) technology, in which a closed needle penetrates a sterile closed container, only opens once inside that container, transfers the fluid, and then self-closes within the container before it is withdrawn from the container. After its withdrawl, the pierced septum self-closes (see **Figure 2**).

This approach was taken to assure that sterilized product and all product contact surfaces are never exposed to the environment or the operator. A combination of materials science knowhow, closed system technology design, and automation permits reliable aseptic transfer without the typical environmental controls associated with other forms of aseptic operation.

Figure 2: Process sequence for Intact self-closing needle (ISCON) filling.



Intact filling has been successfully demonstrated in a controlled not-classified (CNC) environment for the filling enclosure and the surrounding room, an unclassified room where closed processes and their immediate support systems may be located (13). To support its application for use for filling of sterile products, a draft appendix to FDA's *Guideline on Sterile Drug Products Produced by Aseptic Processing* has been published (14).

Since these media fills were run, Medinstill's development team has improved septum design, as well as needle shape, dimension, and external finish. The company has successfully completed sterile media fills through microbial populations of 10^6 colony forming units (CFU)/mL on both the needle and the septum (15).

In the technology's latest design, microbes are excluded by frictional forces that are created where the septum and needle meet at the point of penetration, and which prevent microorganisms from entering the container. These same forces come into play as the needle is removed from the container, preventing any liquid from remaining on the surface of the needle.

The septum's self-closing design also results in the creation of frictional forces along the needle's conical tip so that, even after the needle has been completely withdrawn from the container, the pin hole left in the septum is difficult to discern visually.

In order to ensure container integrity, the tiny pin hole left by the needle in the septum's self-retractable material is immediately re-sealed within the filling enclosure, using silicone drop, hot melt, or laser-heat processing. This step eliminates the need for cap sterilization, as well as for related component transfers, and saves the capital that would be required to invest in a high-speed capping machine. Hot melt resealing, in particular, has the added benefit of assuring tamper-evident sealing of the filling port.

Although the process has been engineered to ensure complete isolation of the product from the filling process, several procedural controls have been added to further mitigate the microbial contamination risk (see **Figure 3**), including:

- Positioning of the ISCON filler in a non-classified restricted access controlled area, using a filtered air supply
- Use of a filtered air supply immediately over the filling zone, and excluding operators from the filling zone while filling is taking place
- Built-in routine monitoring of the total number of particles that are present in the room, to assure control of conditions in the background environment

Figure 3: ISCON filling enclosure.

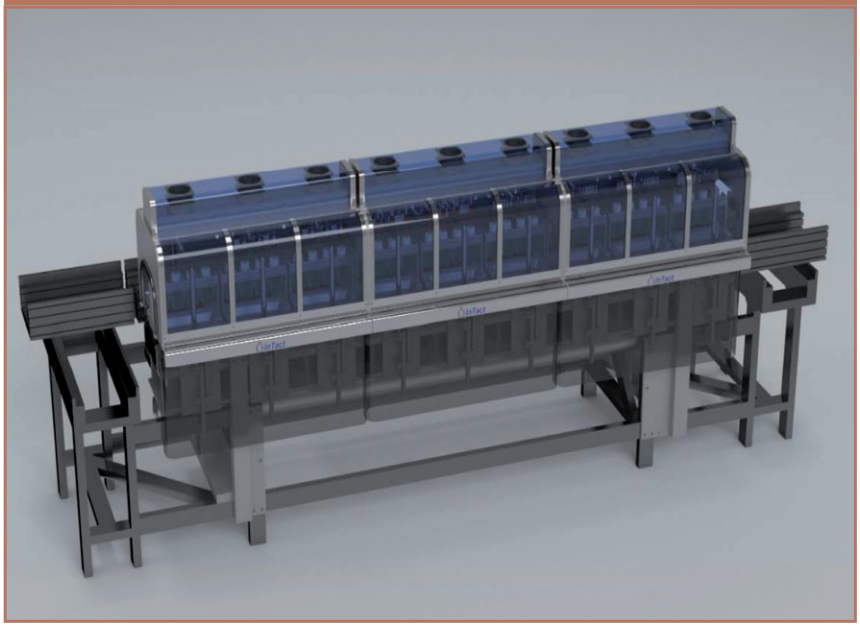
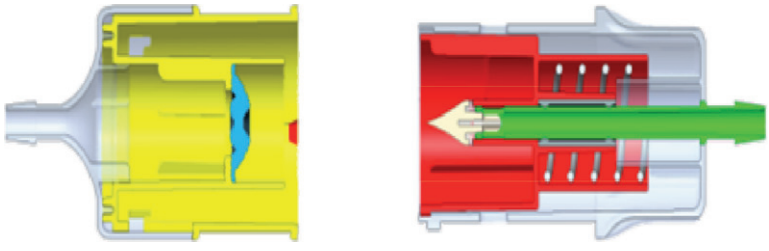


Figure 4: ISCON connector.



- Using radiation to pre-sterilize the disposable filling kit assembly (consisting of ISCON tubing, and sterile ISCON and septum-like connector) and the pre-closed container so that both are delivered to the filling system in sterile bags that are opened in the non-classified environment immediately before use
- Automated removal of the protective needle cap within the fill enclosure
- Visual confirmation of proper container position prior to enclosure entry.
- UV decontamination of the septum surface within the enclosure just prior to filling, in case of manual loading of the pre-sterilized closed containers
- Resealing of the pin hole in the septum created by needle withdrawal within the enclosure using controlled means
- Optional use of a protective over-cap on the septum in a separate enclosure, a step that is not needed when the container is hot melt resealed
- Use of disposable components for product contact throughout the aseptic process.

These measures serve to prevent any contact between the product and the processing environment. The closed, single-use fluid path also eliminates exposure of the product to the operator, so that the ISCON filling process meets Biosafety Level 3 (BSL-3) requirements.

The same ISCON mechanism in the Intact connector facilitates near-continuous aseptic manufacturing by avoiding the need for lengthy changeover procedures between batches (such as clean- and sterilize-in-place operations, environmental decontamination, and line clearance).The filling system has also been designed to fill multiple container types (whether vials, bags, or bottles) with minimal changeover time and can be transported to and installed in new sites, within days.

Use of closed transfer system principles eliminates nearly all of the facility design and operational considerations associated with conventional aseptic processing. In addition, it obviates the need

Table IV: Intact media fills.

Closed needle / Closed vial	Background environment	Fill environment	Media	Media fill results	
				# Units tested	# Units contaminated
Various	CNC	CNC	Various	17,331	0

Table V: Intact media fills with microbially contaminated septum.

Closed needle / Closed vial	Background environment	Fill environment	(CFU/septum)	Media	Media fill results	
					# Units tested	# Units contaminated
Various	Non-classified	Non-classified	4 Log and higher	Various	1,718	0

Table VI: Intact media fills in non-classified environment

Closed needle / Closed vial	Background environment	Fill environment	Media	Media fill results	
				# Units tested	# Units contaminated
Various	Non-classified	Non-classified	Various	54,828	0

for environmental classification and monitoring; environmental decontamination; and the proficiency of personnel in aseptic gowning, filling machine, and line setup and operation.

The filling system's aseptic processing performance has been demonstrated through the execution of a number of rigorous challenges (16, 17). Successful media fills have been performed in a variety of background environments starting with the planned controlled non-classified environment envisioned for commercialization as well as other less closely controlled environments (see **Table IV**). The background conditions for these media fills were intentionally performed under microbiological conditions that are more challenging than those typically used to test conventional aseptic filling systems.

The media fills cited in **Table IV** exposed individual septa to microbial contamination prior to the fill. Additional fills were performed on a limited numbers of units in which the target locations on the components were exposed to microbial populations of over 10^6 CFU (including *S. marcescens, B. diminuta, E. aerogenes, C. albicans and S. epidermis* strains) prior to filling (see **Table V**). Background environments used for these trials varied from ISO Class 7 to unclassified.

Table VI summarizes all the sterile media fills done that have been performed on the filling system to date in non classified environments, including worse-case media simulations. The Intact and ISCON filling technologies have demonstrated the ability to achieve microbial exclusion at levels that have not yet been seen in traditional aseptic processing operations, at conditions that could not be used with other technologies, including Blow Fill Seal, FFS, and robotic filling in isolators.

ISCON would also permit aseptic filling to be accomplished in non-classified environments. This, in turn, would eliminate the need for conventional environmental and other controls.

Potential impact on global health

By eliminating critical surface exposure, the key concern in aseptic processing, closed systems such as Intact could be used in pandemic response and just-in-time medical countermeasures. In addition, the ability to fill vaccines and other therapeutics into pouches and to deliver multiple-dose syringes using an anti-retro-contamination dispenseing valve could make the following possible:

- Filling one billion doses in three weeks at a cost of less than $0.10/dose. Current US government-funded capacity is approximately 50 million doses of preserved vaccine in 12 weeks (17), leaving millions of Americans and billions worldwide unprotected.
- Implementation at a very low capital cost, enabling dedicated lines with the flexibility to respond to pandemics with no interruption of routine filling essential medicines during a global threat.
- Simplified logistics and mass vaccination campaigns with one pouch and syringe (changing needles) for each 50–100 patients.

Tests for applicability for pandemics

The technology is currently being tested to demonstrate its ability to work in pandemic responses for the following:

- Pneumococcal vaccine using a single dose closed vial (18)
- Attenuated virus vaccine using a multi dose closed vial (19)
- Virus-like particles vaccine using a multi-dose closed vial and a multi-dose closed pouch (20).

In short, closed systems such as Medinstill's promise to play an increasingly important role in reducing the cost of vaccine manufacturing and improving facility flexibility, especially as companies in developing markets build their own local manufacturing plants.

As they continue to evolve, closed systems are proving to be disruptive technologies with the potential to change the way that vaccines and other sterile drug products are manufactured in the future. This change promises to bring the pharmaceutical industry closer than it has ever been to sterile processing.

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