

Disposable Technologies for Aseptic Filling

A Case Study

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A global player in vaccine manufacturing, Solvay Pharmaceuticals, has built an influenza vaccine manufacturing facility based on cell culture technology to meet the growing worldwide demand for vaccines. Located in The Netherlands, this facility fills flu vaccine syringes and will also act as a contractor for filling and packaging similar products.

This case study describes Solvay's project management activities for two newly installed high-speed, high-capacity, isolator-based filling lines in the Dutch final filling facility. Key project challenges the company faced when installing these lines included

- a short project timeline
- the need for preventing contamination risk
- flexibility requirements (a multiproduct filling line)
- the need for high throughput (with quick sanitization)
- necessary reliability (three shifts for a June–September campaign)
- validation and revalidation issues relating to multiproduct operations
- limited space (two filling lines, maximum).

Solvay chose to use isolators because contamination risks are too high in conventional cleanrooms for seasonal products. No preservatives are used in the flu vaccine formulation. In addition, this vaccine cannot be terminally sterilized.

MATERIALS TRANSFER

Having chosen isolator technology, Solvay needed to determine how to transfer materials in and out of an isolator without challenging their cleanliness. Materials that need to be transferred include empty syringes, final bulk product in liquid form, stoppers and plungers, environmental monitoring samples, and filled syringes (Figure 1).

Traditional Material Transfer: In a traditional final-filling facility, stoppers and plungers arrive loose and nonsterile in bags. They're unloaded into a special washing machine that carries out washing, siliconization, and sterilization. Other materials are moved into the filling machine using rapid transfer ports. Formulated bulk fluid arrives by a stainless steel vessel that has to be steam-connected to the line. Both transfer line and vessel must be cleaned and sterilized in place (CIP, SIP).

Validation/Maintenance: All those materials require additional validation

and maintenance. Typically a traditional filling line requires two or three months of additional validation just to start it up. That covers CIP and SIP validation of the vessel and transfer line, as well as the stopper-plunger handling system. Additional maintenance costs (related to replacement and labor) are associated with traditional facilities because of the need to maintain vessels, washer, and transfer lines.

Alternative Technology Investigation: Needing to maintain a short project timeline while working in a multiproduct environment, Solvay decided to investigate alternative technologies for materials transfer. The decision criteria for disposable technology were driven by the following:

- no cleaning (and thus no cleaning validation)
- no risk of cross-contamination in a multiproduct environment
- no steam sterilization validation for piping



Photo 1: Solvay Pharmaceuticals' isolator filling line in The Netherlands

- no autoclave-loading validation
- use of presterilized, preassembled components (no manipulations after sterilization).

Isolators allowed use of several single-use technologies: decontamination chambers for empty syringes; a disposable bag system for bulk fluids; rapid exchange ports from Isolateur Dénominateur Commun (IDC, www.idcbio.com) for transfer of fluid, stoppers and plungers, and environmental monitoring samples into and out of the isolators; and “mouse holes” for transfer of filled syringes.

THE DISPOSABLE TECHNOLOGY

For this filling line, isolators are housed in a Class D environment. Photo 1 shows the Solvay filling line based on disposable technologies used to fill syringes with flu vaccine. The facility incorporates two filling lines rated to fill 18,000 syringes per hour. Empties arrive at the filling line in sealed tubs, each of which contains 200 syringes. A total of nine tubs (1800 syringes) are loaded into a decontamination unit, which cleans only the outside of the container because the syringes inside are clean and sterile.

As Shown in Figure 2: When the tubs enter the “peeling” section, a top plastic layer is peeled off to reveal sterile syringes. Those move into the filling section, where they are filled (for the flu vaccine, a 0.5-mL fill). A stopper is then applied to each syringe to seal the product formulation inside, and then a separate plunger is added. Filled, sealed syringes then leave the isolator in their tubs.

Gamma-irradiated plungers and stoppers arrive in their own disposable bags, which come with an IDC beta Biosafe docking port. A bag is docked to the isolator and unloaded internally into feed hoppers. All in all, it takes 1.5–2.0 hours to prepare the line.

Highlighted disposable technologies for the filling line include the following:

- IDC Biosafe rapid-transfer ports for both solids and aseptic fluids transfer onto the line, allowing disposable bags to be docked to the isolators
- 500-L disposable Flexel 3D brand bags from Stedim (www.stedim.com) for storing the bulk flu vaccine

Figure 1: Materials transfer into and out of an isolator filling line

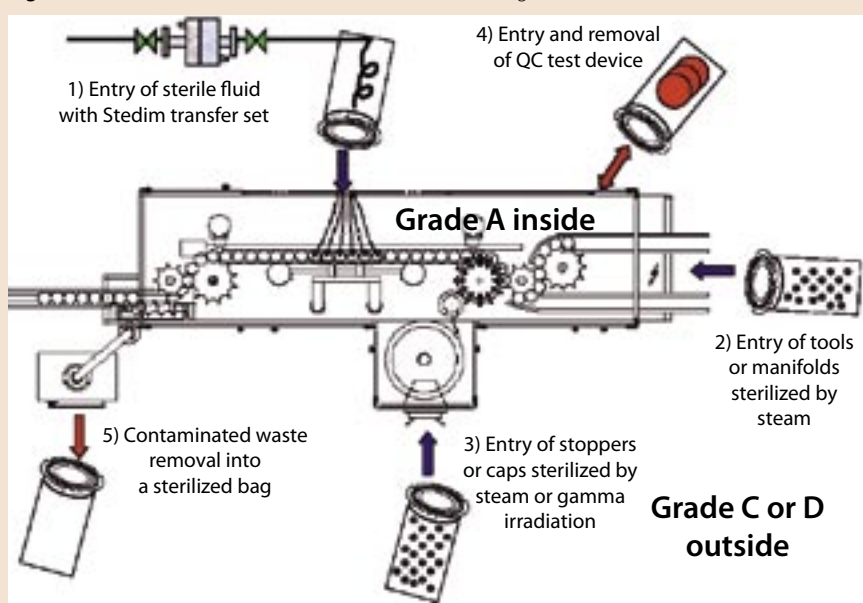
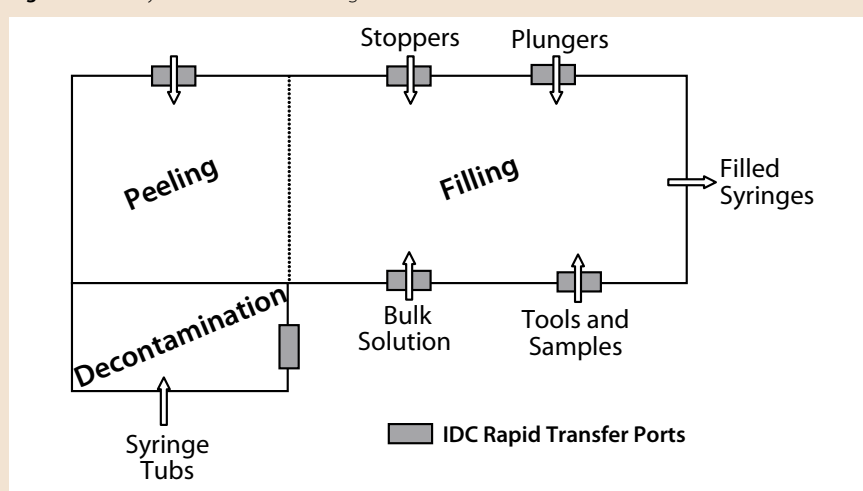


Figure 2: Solvay Pharmaceuticals' filling line



- Kleenpak brand connectors from Pall Corporation (www.pall.com) for rapid aseptic fluid flow connections.

The disposable bags, transfer sets, connectors, and rapid-transfer ports were delivered preassembled and gamma sterilized, ready for aseptic fluid transfer. Because of this preassembled, totally closed, gamma-sterilized single-use system, no class-A laminar air flow is necessary. Six IDC rapid-transfer ports allow all necessary entry of the isolator filling line.

Fluid Transfer: Fluid is aseptically transferred from the disposable Flexel 3D bag into the isolator by a Stedim rapid aseptic transfer system (RAFT), using in this case an in-line combination of the Pall Kleenpak aseptic connector, a transfer set, and the IDC Biosafe rapid exchange port.



Photo 2: A Flexel 3D bag and Palletank vessel are shown with a transfer set and IDC alpha and beta Biosafe ports docked to the Solvay Pharmaceuticals isolator filling line.

Figure 3: The IDC Biosafe port and rapid aseptic transfer port in operation

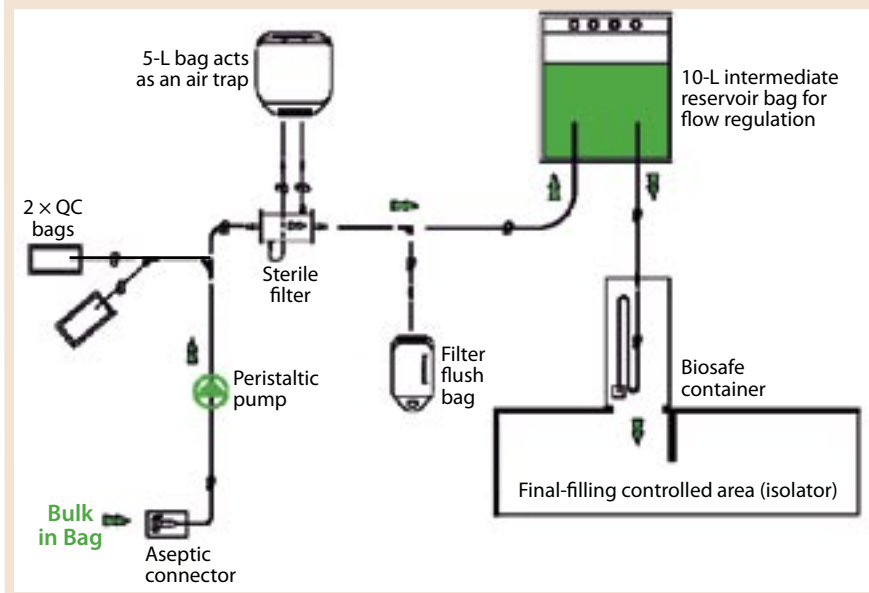


Figure 3 illustrates the fluid transfer process. A gamma-sterilized bag arrives with its aseptic connector and transfer set attached. After QC samples are taken, fluid is pumped to the sterilizing filter, with a 5-L Flexboy bag acting as a vent (Solvay requires a closed-bag system for venting to prevent sterility compromises). Further along the line, a Flexboy bag collects the first half-liter of bulk liquid that rinses the filter. A specially designed 10-L intermediate bag acts as a reservoir for regulating the amount of buffer that feeds onto the syringe filling line. It is connected to the isolator through an IDC alpha/beta Biosafe door and Kleenpak connector.

Transfer of Stoppers, Plungers, and Samples: As mentioned, in a

traditional filling line the stoppers and plungers arrive loose and nonsterile in bags. They are unloaded into a special washing machine that washes, siliconizes, and sterilizes them.

COST COMPARISON

Part of Solvay's project analysis was to evaluate the relative economic attractiveness of the disposable and traditional filling technologies. A cost-of-goods (COG) model was developed for both the disposable and traditional reusable filling facilities by expert consultants in economical modeling (Biopharm Services, www.biopharmservices.com). Based on a Microsoft Excel spreadsheet, the model breaks down the following cost categories (Figure 4):

- capital charges

- consumable costs (disposable bags, connectors, stoppers, plungers, and spares)
- material costs (chemicals, WFI, purified water, and steam incurred in running the process, cleaning, and sterilization)
- labor costs (direct production, quality, and maintenance).

The COG model estimates the cost differences between disposable and traditional filling technologies, which allowed Solvay to compare the two methods for cost effectiveness. Costs are expressed per batch for each option. In addition, savings for each category were calculated to identify where cost differences occurred. A case study was presented for evaluating the relative economic feasibility of a disposable filling facility and a traditional reusable facility. In Table 1, negative values occur where the disposable option is more expensive than the traditional facility.

These model results show that disposable filling technology is more economically viable than traditional reusable technology. The single-use option benefits from reduced capital charges (48%) because of lesser equipment requirements. Its disposable nature eliminates the need for cleaning and sterilization. So the disposable filling facility benefits from lower operating costs incurred for the material and labor cost categories (cost reduction estimated at 5% and 25% respectively). However, there is a 37% increase in the costs of consumables because of the presterilized and ready-



Photo 3: In the Solvay facility, plungers and stoppers arrive gamma-irradiated and contained in a disposable bag that has an IDC beta Biosafe port to dock with the alpha Biosafe on the isolator for aseptic transfer.



Photo 4: Environmental monitoring (EM) samples can be transferred from the isolator through an IDC beta Biosafe port system.

to-use stoppers and plungers sold in disposable bags. Although the disposable option has higher consumable costs, its overall running costs are 41% lower than those of traditional reusable technology.

Solvay carried out a sensitivity analysis to investigate the effects of various scenarios on COG savings for the disposable filling option. This enabled decision-makers to examine the variability of key input parameters on those cost outputs.

Sensitivity analysis provides an organized and systematic way to investigate the impact of key input parameters on the stability of a base case. Biopharm Services carried out a sensitivity analysis for Solvay to investigate the effects on COG for both a disposable and a traditional filling facility. A sensitivity analysis was then carried out for each variable in those scenarios, keeping all other variables fixed at the baseline value each time. In Scenario A, batch size was reduced to 200 L. In Scenario B, syringe fill volumes were increased to 1 mL. Table 2 summarizes the cost savings. Cost values are for the single-use system relative to the traditional reusable option.

In scenario A, with the batch size reduced to 200 L, an overall savings of 60% is estimated for the disposable filling option. Reduction of batch size has increased the cost savings 19% from the base case. The model results indicate that for scenario B, in which the syringe fill volume is increased to 1 mL, a 58% cost savings is realized for the disposable filling facility.

Benefits: This kind of COG model offers several useful functions. Users can define key input parameters and view resultant cost outputs. The model provides a breakdown of COG in different cost categories. Decision-makers can evaluate process economics for the two filling technologies and perform sensitivity analyses of key input variables to determine their impact on cost.

Certain additional factors were not calculated in that analysis: Faster turn-around times translate to higher throughput when working with disposables.

Table 1: Cost breakdown

Cost Category	Disposables	Traditional	Cost Savings	
			Per Batch	Percentage
Capital	40	54,196	54,156	48%
Consumables	58,368	17,013	-41,355	-37%
Materials	0	5,310	5,310	5%
Labor	8,266	36,387	28,121	25%
Total	66,673	112,905	46,232	41%

Table 2: COG results of the sensitivity analysis

Cost Category	Scenario	
	A	B
Capital charges	63%	60%
Consumables	-26%	-27%
Materials	3%	4%
Labor	20%	21%
Total	60%	58%

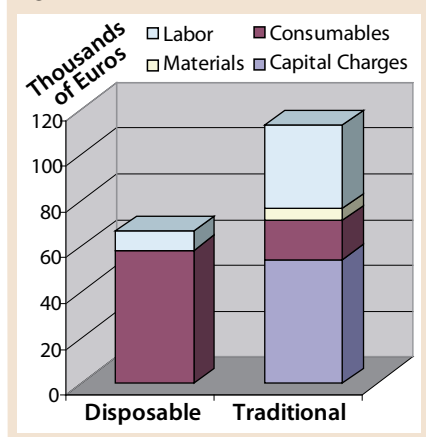
In a facility working with traditional technologies, COG rises dramatically as plant use drops — so the COG benefits of disposables are even greater with lower overall use. Using disposables allows you to divert fixed capital costs into variable consumables costs, which helps manage uncertainty such as whether the filling lines run at full capacity for contract manufacturing outside the seasonal flu vaccine filling activity. This is important when evaluating the use of disposable technologies, if you consider that capacity use for all biomanufacturers with mammalian cell culture systems is currently 68.8% (2). In a future article, we plan to address this in more detail.

INTERIM RESULTS

To date, 250,000 syringes have been successfully filled in this facility, and they were all successful. More than 100 Kleenpak and more than 4000 Biosafe connections have been made. The technology continues to be fine-tuned, with development of a disposable filling station in progress. An additional benefit of working with disposable systems is that design optimization can be carried out very simply without having to take out existing equipment.

By working with disposables technology, Solvay has developed two highly efficient and safe multiproduct filling lines. The sterile production manager says, “I would definitely choose the same approach again.”

Figure 4: Cost breakdown



SOME FILL-AND-FINISH TERMINOLOGY USED HERE

- alpha port:** transfer port mounted on a cleanroom or isolator wall
- beta port:** mobile container port that connects to an alpha port for transfer
- mouse hole:** open space (generally small) between two different zones; protected from contamination with a dedicated air flow system
- peeling:** peeling off of a Tyvek face welded onto a tub (container)
- siliconize:** coating stoppers and plungers with silicone to facilitate their entry into syringes

REFERENCE

1 Langer E, Ranck J. Capacity Bottleneck Squeezed By Downstream Processing. *BioProcess International* 4(3) 2006: 14–18. 🌐

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