Single-Use Technologies Bring Flexibility to Final Filling Operations

Successful Integration of a Disposable Liquid Filling System

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Recent research and new innovative technologies have contributed to an increase in the number of new vaccines becoming available. Although the use of disposable technologies can bring more flexibility to a manufacturing process, potent innovative viral vaccines demand specific care during handling operations throughout all steps of clinical materials manufacture.

Even with single-use filters and silicone tubing, dispensing parts require manual installation, steam sterilization, and cleaning of all piston pump parts and needles. As part of the increasing trend toward disposable assemblies, a self-contained solution for final filling has been developed for easy implementation with existing filling lines. BioProtect Research — now Vibalogics GmbH (for *viruses, bacteria,* and *biologics*) — has successfully and easily integrated such a disposable liquid filling system into an existing filling line.

Product Focus: All biologicals

Process Focus: Downstream (fill and finish)

Who Should Read: Process engineers, manufacturing, and facilities and fill–finish managers

Keywords: Disposables, fill and finish, fluid handling, aseptic processing, outsourcing

Level: Basic

Improving Process Efficiency:
Vibalogics is a contract manufacturing organization (CMO) located in the north-German town of Cuxhaven. The company specializes in research and development and CGMP manufacturing of immunological products for veterinary and human medicine, with viral and bacterial vaccines as its core competence. During the past few years, the company has continually renewed its manufacturing processes to increase safety and performance, either by acquiring new equipment or by integrating new technologies into existing machines.

Following that plan, Vibalogics focused on improving efficiency and yield of its filling process. Companies responsible for the filling operations of new drugs in clinical trials have to deal with small and very diversified lots, which necessitates repetitive, accurate cleaning procedures, especially for viral vaccine applications. In an ideal solution, all drug-contact parts would be disposable. Beginning with this ideal concept in mind, Vibalogics decided to integrate a single-head liquid filling system: the Acerta DS1 dispensing system from Millipore Corporation of Billerica, MA (www.millipore.com).

The Dispensing System

The Acerta DS1 dispensing system is a closed sterile disposable assembly with two main parts:

- a preassembled, sterile, single-use filling module consisting of a product reservoir with tubing, fittings, and a filling needle, all of which are disposable

Photo 1: Acerta DS1 dispensing system integrated in an automatic filling line

- stainless steel hardware equipped with capacitive and optical sensors and pinch valves, to which the single-use module is installed.

All hardware parts and sensors are in contact with the outer surface of the disposable unit, preventing any risk of their contacting the inner sterile surface that that contacts (or touches) the drug.

This dispensing system is both gravimetric and volumetric. The drug is transferred by peristaltic pump into a reservoir bag, in which the liquid level is controlled by a capacitive sensor that drives the peristaltic pump on and off. Liquid contained in the reservoir fills a vertical measurement tube by gravity (Figure 1A). A pinch-valve system and optical level sensors control measurement of the tube-filling step. Once the upper optical sensor detects the specific height of liquid in the reservoir, the upper pinch valve is closed and feed stops. Simultaneously, the lower pinch valve opens and positions itself on

the tubing to dispense through a disposable needle (Figure 1B).

The dispensing volume is controlled either through changing the internal diameter of the measurement tube or by changing the distance between the two optical sensors positioned along that tube. The two optical sensors are typicall set up before the fill step is run because the system is primed by a remote hand-held control panel linked by a cable into the dispensing unit. Those optical sensors are unaffected by drug color or transparency.

Integrating the System into Existing Filling Lines: Seamless integration of the Acerta DS1 dispensing system into existing filling lines is ensured by a basic "hand-shaking" protocol between two pieces of equipment: The Acerta dispensing system dispenses only when specific conditions are met, then a signal is given to the filling line so vials will move forward.

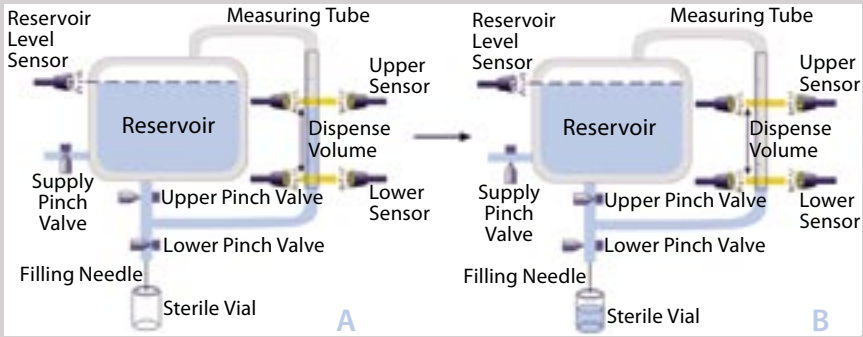
Qualification of the dispensing system technology at Millipore Corporation includes filling performance over four consecutive hours of dispensing along with extractables analysis and particle-release characterization (see the "Filling Performance" box). The drug-contact materials involved are well known and have been used often in pharmaceutical manufacturing operations:

- silicone Pt for tubing
- Pharmapure tubing from STI Flow (www.stiflow.com) for the pumping tube
- Ultralow-density polyethylene (ULDPE) for the reservoir bag
- high-density polyethylene (HDPE) for all adapters
- polycarbonate for the needle.

At the Vibalogics plant, Millipore tested and verified that all plastic components met USP class VI requirements (**1, 2**) both before and after gamma irradiation.

Concerning the performance test at Vibalogics, the dispensing system proved its ability to successfully dispense volumes within 0.2 mL and 10 mL, with accuracy of <0.5% in weight. The system hardware integration was completed without major modifications at an existing filling line. It was electrically wired to the existing line using input/output (I/O) cables that come supplied with the hardware and following the precise instructions contained in the Acerta system user guide. Other mechanical modifications of existing filling line equipment were unnecessary because the dispensing system is located on the bench of a wheeled trolley cart. That allows for easy installation of the expansion and remains outside the laminar air-flow (LAF) hood because the disposable unit is closed. Once the system was settled and ready to be filled with the drug, the still-covered needle was passed through the the LAF cabinet into the restricted class A filling area and positioned into the needle holder. The system was then ready to dispense (Photo 1).

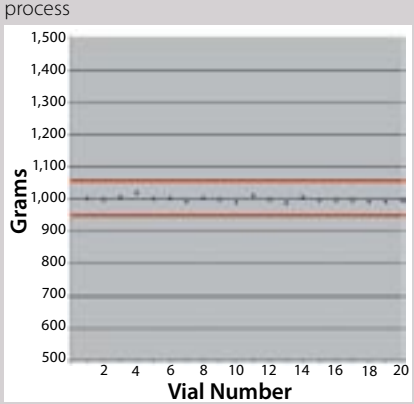
Figure 1: Functioning principle of the Acerta dispensing system technology: A) intake cycle; B) dispensing cycle



Filling Performance

GMP batch record shows three fills (two to four hours) at a filling speed of ~2,000 vials/hour with a continously running hygienic monitoring of air particles directly next to the filling needle. The Acerta disposable module particulate levels are within specifications set forth in USP <27>, section 788. Samples exhibited <10 ppm total organic carbon after liquid contact surfaces undergo a static soak for 60 minutes with lysate reagent water (**1**).

Figure 2: Accuracy of 20 vials during a filling process



Installation and operational qualification (IQ and OQ) were performed in collaboration with Millipore, and performance qualification (PQ) was executed during media fill trials by Vibalogics. Figure 2 shows that the dispense volume remained accurate over time.

Vibalogics tested for sterility through three consecutive runs using a sterile culture media, CASO Bouillon from VWR International LLC (www.vwr.com). This casein soja peptone is a typical complex medium in which bacteria will grow and is very often used as a worst-case scenario for these process simulations. The maximum accaptable limit for contaminations would be 1 out of 3,001 vials. We passed the test with the Acerta DS-1 system, showing no contamination in 10,000 vials (1 mL per vial dispensed) at 2,000 vials/hour. These three runs verified that the new technology was successfully integrated into the process (data not shown). The integrated technology should not introduce additional handling operation to the operators, so it does not increase the risk of contamination. The three media fill runs concluded with zero positives.

The system did have a light suck-back affect, which prevented the needle from dripping. Furthermore, because filling is by gravity, no formation of aerosols occurred when using traditional piston pump systems.

Benefits

The Acerta dispensing system technology is particularly beneficial for filling small clinical batches because it facilitates change-over between batches. The single-use component is discarded after each filling operation, which eliminates the need to clean and sterilize product-contact parts. That provides

Photo 2: The Acerta DS1 dispensing system as an integrated unit in a fully automated filling line for 1,000–10,000 vials/batch.

Photo 3: The Acerta DS1 dispensing system used a stand alone unit

savings in time and cost, and it offers higher security of product and personnel.

For each batch, adjustment of the fill volume is easy and can be made at any time. Four different disposable modules are available to fit specific applications and dispense weight ranges, and the software automatically adjusts the height of the upper sensor. For large batches (greater than 1,000 units per filling), the dispensing system is integrated into a filling line (Photo 2), whereas for smaller batches (>1,000 vials), the Acerta dispensing system fills vials manually into a biocabinet (Photo 3). An operator can use both hands to move vials because the dosage is ensured by a pedal switch, which is provided as part of the accessories.

Installation is easy. The integration of this dispensing system into an existing filling line was successful and profitable for Vibalogics. And the Acerta dispensing system technology can be scaled up to multiple-head lines, which improves speed to market.

The system allows greater flexibility in filling operations, particularly with potentially dangerous drugs such as viral vaccines and compounds that are toxic in large doses, and for which security and protection for both personnel and product are necessary. CMOs and other companies can benefit from rapid equipment change-over between filling campaigns while preventing cross contamination.

References

1 Lit. No. VG1800EN00, Rev. 06/2005. *Validation Guide: Acerta Disposable Module.* Millipore Corporation: Billerica, MA, 2005; 29–30.

2 USP <88> Biological Reactivity Tests for Class VI Plastics. *USP–National Formulary.* United States Pharmacopeial Convention: Rockville, MD; www.usp.org.

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