



## Packaging Challenges in Pharmaceuticals

John Williamson, Contributing Writer -- 9/3/2007

Today's pharmaceutical labs and manufacturing facilities are extremely costly and complex, requiring stringent process controls in an environment that has two functions: protecting personnel from the product being manufactured and protecting the product from contamination.

That's because many pharmaceuticals are characterized as aseptic potent, aseptic cytotoxic or radioactive radiopharmaceuticals, meaning they can have an extremely adverse affect on personnel should they be exposed. Similarly, because purity is paramount, drugs must be protected from contamination during the manufacturing and filling operations.

Such drugs are manufactured and packaged by the major pharmaceutical houses and by contract manufacturers under extreme controlled conditions provided by isolation systems that conform to industry standards cited in the [Food and Drug Administration \(FDA\)](#) guidelines.

Isolation systems represent an evolution in traditional large-area cleanrooms by providing dedicated enclosures with an ISO class 5\* critical zone where fill-finished operations take place. Depending on which type of system is used, they are placed in an ISO class 7 or 8 surrounding room. Significant economies are offered compared to traditional cleanrooms requiring filtered air, personnel gowning, air locks and other protection procedures.

### Bubble-Free Filling™ for Pre-Filled Syringes

"Pharmaceutical and biotech companies involved in new drug development face mounting cost and safety issues due to the nature and use of products," says Shawn Kinney, president of [Hyaluron Contract Mfg.](#) (HCM), Burlington, MA. "Cost is an issue for many, given the rising expense involved in drug development and manufacturing. Some active pharmaceutical ingredients, or API, can cost thousands of dollars per gram and must be administered in fairly small sizes. Waste of any kind can be quite costly not to mention potentially hazardous to the patient.

"Safety, too, is a concern," Kinney says, "given the many opportunities for microbial contamination that a product is exposed to from the door of the manufacturer to the end user. Safety also applies to ensuring that the proper dosage is administered to the patient."

These concerns have led Kinney and the engineers at [HCM](#) to develop a revolutionary new way of filling and stoppering prefilled syringes — known as Bubble-free filling™ — that enhances dosing accuracy and improves product sterility assurance.

In conventional, or traditional, processes, prefilled syringes are filled and stoppered under ambient atmospheric conditions. First, a needle is inserted into a syringe and product is expelled into the syringe. Next, a stopper is forced through an insertion tube which is placed in the syringe above the liquid level line. A rod within the insertion tube then pushes the stopper into the syringe, creating a sterile barrier between the product and outside contaminants.

"With this traditional filling and stoppering method," Kinney says, "the headspace left inside the syringe may be unacceptable considering what we have seen to be ever smaller dosing volumes with today's potent drugs."

For one thing, Kinney says, air left inside a syringe can under certain conditions such as reduced atmospheric pressure, expand causing the stopper to "rise-up" into the non-sterile area of the syringe.

When the reduced atmospheric pressure returns back to, or close to, the original atmospheric pressure at which the syringe was filled and stoppered, the stopper “drops back down” or returns to its original position. This “spring-like” phenomenon of the headspaced air bubble creates the situation where the stopper rises up into the non-sterile portion of the syringe barrel potentially dragging contaminants back down with it during the drop-back-down process. This would happen, for example, when a syringe is shipped via air or at high ground altitudes.

### **Product Wastage and Safety Issues**

Further, air trapped in a syringe can cause some of the product to leak out through the needle when the tip cap is removed, exposing the end-user and administrator to potentially hazardous materials. “Moreover, in cases where the dose required is small — volumes of 0.5 ml or less, for example — any lost product can be significant in delivering the full volume prescribed,” Kinney says.

### **Designing a Bubble-Free Filling™ System**

HCM was established to manufacture products made from hyaluronic acid, a viscous product that is resistant to flow. Using equipment manufactured by [Inova Pharma](#), HCM developed a process for filling hyaluronic acid into syringes for use in orthopedic procedures and eye surgery, among others.

The company was approached by a customer who had an oxygen sensitive, aqueous or non-viscous product and had asked HCM for potential solutions. “By retrofitting the Inova equipment,” Kinney says, “we were able to develop a two-stage process that allowed for the bubble-free filling of aqueous as well as viscous products.” And so was born the company’s Bubble-free filling™ technology.

Bubble-free filling™ involves a two-step on-line filling process. In the first stage — online vacuum filling — a suction cup is placed over the syringe and a vacuum is pulled to evacuate air from the syringe and needle stake. During this stage, the product is expelled into the syringe, replacing the air that was previously evacuated.

The filled, unstoppered syringe is then indexed over to the next stage of filling — online vacuum stoppering — where a suction cup again applies a vacuum, removing any gas from the product as well as any air that remains in the free space above the product surface. At this point, the stopper is inserted, the vacuum is released and the stopper is pushed by differential pressure into direct contact with the product, eliminating the gas headspace and providing a bubble-free container.

“This process greatly enhances the benefits of a pre-filled syringe including dosing accuracy, product safety and sterility,” Kinney says. “That’s why we feel fairly confident that as our customers reap the benefits of bubble-free filling™, both in terms of cost and safety, the process will catch on and may one day become the industry standard.”

\*ISO Class 5 provides an environment where particulate count 0.5 microns and larger is limited to 100 ft<sup>3</sup>. ISO 7 = 10,000 ft<sup>3</sup>; ISO 8 = 100,000 ft<sup>3</sup>.

### **Designing an Explosion-Proof Aseptic-Cytotoxic Filling Line**

Additional design challenges arise when the manufacturing process for a pharmaceutical product involves the use of volatile solvents. Such is the case at [Pierre-Fabre Médicament](#), Pau, France, a manufacturer of proprietary drugs and a contract manufacturer of existing and new next-generation aseptic cytotoxic cancer drugs. The company operates one of the most advanced aseptic cytotoxic facilities in the world.

“Issue one is the absolute necessity of a thorough cleaning of our ISO Class 5 isolators used in the manufacturing and filling lines to eliminate the danger of cross-contamination while providing worker and environmental protection when we change over to another product,” says Pierre-Fabre's Paul Martin. “The potency of the cancer drug is such that we essentially developed a new generation of isolators that meet the cleaning criteria.

“Complicating the issue,” Martin says, “the drug is manufactured with ingredients that are non-soluble in water. In this instance, ingredients are dissolved in a 99 percent alcohol solution that is then removed using a freeze-drying (lyophilization) process that by its nature causes the release of explosive vapors during the drying cycle. Vapors can also be released during the compounding and vial filling cycles.”

Operational procedures are governed by the [ATEX Directive \(for ATmospheric EXplosives\)](#), a combination of two European directives associated with equipment used in and people who work in potentially explosive atmospheres.

“Sterility issues came first as we addressed the means to insure the total absence of cross-batch contamination by using WIP (wash in place) and VHP (vaporized hydrogen peroxide) sanitization processes,” says Martin (see Figure 2, above right). “Working with our supplier SKAN AG, we developed major design changes that included evaluating materials of construction for and placement of static nozzles and spray guns and post fill-and-dry vial wash down to remove any contaminants before they are handled. A no-touch liquid waste system insures personnel cannot come in contact with process wastes.”

### **Process Flow**

Vials are washed in the vial washer then pass through the depyrogenation tunnel for sterilizing under high temperatures before transfer to the aseptic filling/stoppering area. Design criteria for the filling process includes controlling the isolator temperature, the humidity and atmospheric pressure and loading the freeze dryer shelves at a low temperature.

Vials are filled with the solution and half-stoppered with fluted stoppers before being transferred to the freeze dryer. During these operations volatile fumes could be generated as the alcohol solution evaporates via the flutes in the stoppers and where vapors could reach an explosion point. To avoid this, a special air pattern flow was designed to capture and monitor vapors concentration to maintain ISO class 5. The isolator atmosphere is purged before passing through double HEPA safe-change filters that protect personnel from any inadvertent contamination and protect terminal filters in the isolator.

Stacked shelves of the half-stoppered vials are subjected to vacuum and freezing. The vials now contain the dry residue that is the drug. When dry, the bottoms of the shelves seat the stoppers in a shelf below thereby providing fully stoppered vials for removal.

Still in the isolator, vials are capped then externally washed and blow dried to remove any residue that may adhere from the freeze-drying process. They are then readied for inspection, labeling, packaging and shipment.

### **Author Information**

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