

Source: Pharmaceutical Commerce – June 2005

Parenteral Packaging Goes Pre-Filled

By Greg Valero



Pre-filled injectable devices offer better safety for patients and caregivers

It's no secret parenteral drugs took giant steps towards treating various injuries and diseases the past few years. Delivery systems grew nearly as fast, as new technology, configurations and materials expanded packaging options for pharma suppliers.

Indeed, the parenteral drug delivery system business is on pace to grow 11% annually to \$30.7 billion in 2007, The Freedonia Group (Cleveland) reports. Leading the charge is pre-fillable syringes, positioned as a fast-growing alternative to conventional glass vials and stoppers. Pre-filled systems are gaining wider acceptance in critical, diabetes and emergency care medication, according to the market researcher.

“The movement towards pre-filled syringes is gaining momentum as drug manufacturers find ways to reformulate, avoiding the high costs associated with the lyophilization process,” observes Michael Bergey, VP, business development, packaging services, at Cardinal Health (Dublin, OH). “Pre-filled syringes provide a tremendous benefit to the care giver and/or patient by eliminating the reconstitution step, saving time, increasing safety and compliance, and ultimately, decreasing costs.” Cardinal, which produces liquid and lyophilized (freeze-dried) products, more than doubled its sterile manufacturing capacity at its San Diego facility about two years ago.

Parenteral drug packaging is driven by health care providers' reduction in medical personnel, putting more patients in a position to self-administer their medications without professional

supervision. These applications require failsafe drug delivery systems to prevent contamination and ease injection by non-professionals. Experts say this trend has contributed, in part, to the growth of syringes and “pen” systems with hidden needles for self-injection.

While pre-filled syringes represent a leap forward in convenience for patients, the expansion of biotechnology-derived protein and peptide drugs, antibiotics, chemotherapeutic agents and other compounds administered as sterile injectable products has created numerous opportunities for cost-effective manufacturing and delivery technologies. For example, Becton, Dickinson and Co. (BD; Franklin Lakes, NJ) reports that clinical trials for its new BD Hypak Physiolis found the glass pre-fillable syringe system to be very user friendly. “Participating nurses reported that it took 70% less force to penetrate their subjects’ skin than before,” says Vlada Danner, a BD spokesperson. “The patients reported a 40% decrease in perceived pain associated with injection.” In a related development, BD now offers smaller sizes of its BD Sterifill SCF plastic pre-fillable syringe system in BD Crystal Clear Polymer.

Pre-Filled for Safety

Pre-filled syringes, both aseptically filled and terminally sterilized, although more expensive and with a slower manufacturing throughput than the traditional vial and stopper presentation, have shown significant growth over the last few years. “Ease-of-use, safety and alternate care setting options--such as home use--are strong drivers for pharmaceutical and biotech companies to formulate their new drugs to be stable in a syringe presentation,” says Raymond Scheire, general manager, Taree Pharma (Princeton, NJ), a marketing and technical consulting firm specializing in sterile/aseptic packaging challenges in the pharma, biotech and medical device industries.

Aseptic Technologies (Les Isnes,) claims its new aseptic filling technology, CVFL, takes up the new regulatory challenge for aseptic filling of liquid sterile injectable products. A ready to fill, gamma sterilized, closed vial featuring a fully secured stopper provides a filling process that consists of piercing with a filling needle and resealing with a laser. CVFL completely minimizes exposure of the inside of the vial/stopper to outside contamination, the firm says, and provides a sterility assurance level that is equivalent to isolator systems.

Pre-fill syringes offer a quick drug delivery, experts say, as users

or health care professionals avoid the hassle of extracting the drug from a vial prior to injection. The only impediment to wider use of pre-filled systems appears to be price; Freedonia estimates costs are 25% higher than meds packed in vials and ampuls.

“Premium priced injectable drugs, such as cancer drugs and many biotech drugs, are considered specialty pharma,” Scheire points out. “The enhanced packaging provides functionality, a strong brand image and the packaging cost often represents a small fraction of the overall drug price.”

While borosilicate glass has long been the packaging material of choice for drugs administered by injection, plastic is making inroads in certain applications--such as emergency medicine--due to glass fragility issues. In other sectors, the material is gaining momentum as a viable alternative to glass vials for a variety of reasons. “Companies either want the breakage resistance of plastic, which can give them an advantage in the market, or the inertness of plastic,” observes Don McMillan, vice president of marketing, West Pharmaceutical Services (Lionville, PA), a drug delivery company. “We see efforts to seriously evaluate and use plastic containers.”

One reason why glass was preferred over plastic is because the nature and contents of glass have traditionally been better defined and understood. It maintained lower levels of extractables or leachables--such as ingredients, impurities, contaminants and degradants--that have the potential to accumulate in the product as well as the surface of the packaging.

Extractables Testing

“In some ways, glass is easier to work with from a regulatory point of view,” notes Dana Guazzo, founder of RxPack LLC (Bridgewater, NJ), a package development consulting firm. “You have compendial test methods that support the use of glass. Sometimes extractable testing is less complicated with glass than a plastic material.” Contaminated drugs could harm patients and result in product recalls costing the pharma manufacturer millions of dollars. “Sometimes when you use a low grade plastic material, it can interact with the drug product, causing leachables,” McMillan says. “This can lead to a lot more analysis, more science applied to plastic materials as well as analyzing the interaction of the drug with packaging materials.”

West Pharmaceutical claims that laminated closures based on its West FluroTec barrier film technology significantly reduce

leachables, extractables and particulates resulting from stopper-drug interaction while maintaining seal integrity and reducing the potential for drug contamination. The fluorocarbon film, made from a modified ethylene-tetrafluoroethylene (ETFE) copolymer, helps maintain the full strength and shelf life of packaged drugs by reducing absorption and adsorption of the drug product and providing an effective barrier against organic and inorganic extractables.

“The needs of the biotech industry are driving parenteral drug packaging,” McMillan says. “People are coming up with films, coatings or inert plastic materials that won’t react.”

The rules of the game are changing, industry watchers say, as some newer types of pharma products have problems with glass. These packages may contain free alkali oxides and traces of metals. Throw in the fact there is a growing number of proteins and peptides used as therapeutics and package-product interactions are gaining more attention now than in the past.

“As proteins are used with biopharma products, there have been discussions about the stability of certain biopharma products if they are stored in glass,” says Thomas Petzel, marketing and sales manager for Topas COC at Ticona (Florence, KY).

Shatter-Resistant Plastic

New plastic alternatives, such as cyclic olefin copolymers (COCs), are being widely marketed for sterile pre-fillable syringes. The materials are said to offer many benefits, including low weight, shatter resistance during filling or use, and high barrier properties. “For syringes and vials, cyclic olefin copolymer materials have gained considerable market share versus traditional borosilicate glass,” Cardinal’s Bergey says. “While COC does not have the barrier characteristics of glass, its low adsorption rates and exceptional clarity make it a good choice when applicable.”

Ticona, a producer and marketer of engineering polymers, is making a push to establish COC as a material of choice for pre-filled syringes and vials. The firm claims its Topas COC is ideal for medical packaging because it offers a combination of clarity, moisture barrier, high purity and inertness. Advanced Biomaterial Systems (Chatham, NJ), a provider of biomaterial mixing and delivery systems, recently specified Topas for creating the mixing chamber and syringe in its Plexis Bone Void Filling System, used by surgeons to mix and deliver biomaterials during skeletal-

related procedures.

“The COC’s glass-like clarity allows surgeons to see when the biomaterial is fully mixed and to gauge the amount of biomaterial delivered to the site,” says John Carr, COO, Advanced Biomaterials Systems. “The resin withstands pressures in the syringe that can approach 1,200 psi as the plunger moves the biomaterial down the syringe and through the cannula.”

Since compendia standardization of plastics for parenteral packages reportedly does not exist, for the most part, plastic components must show compatibility with drug products through stability studies. The safety of package constituents must also be evaluated in terms of the risk to patients considering the route of administration and duration of product use, experts say. “You need to make sure the package delivers the protective and functional characteristics that are necessary,” RxPack’s Guazzo notes. “For example, the package should be designed around the need to protect the product from reactive gases, light, moisture, leakage, or microbial ingress, as the product’s specifications and stability profile dictate. You also have to design the package so that it can properly and optimally deliver the drug to the patient in its anticipated setting of use, whether that be in a hospital, clinic, or home environment.”

Guazzo cautions pharma companies against choosing packaging materials based solely on cost considerations. For example, “Cost is certainly important, but you need to weigh any cost savings against the potential risk to the product,” she says. “Parenteral products may cause more problems than they are worth. Package improvements for parenterals should first focus on the benefits offered to the product and/or to the end-user.”