Wave of the Future

Prefills Emerge As a Major Growth Market

by Thomas Otto

Over the past decade, many companies have begun to focus on new approaches such as life-cycle management to enhance the competitiveness of their existing products. This is due to the growing stringency of regulatory parameters coupled with a decline in the number of new and guaranteed successful drugs in pharmaceutical and biopharmaceutical pipelines. Delivery methods are often examined with particular care and then improved for "next-generation" products. In the case of parenteral drugs, the use of prefilled syringes, cartridges, or vials is enjoying a strong rise in popularity. Prefilling has a great number of advantages, including improved safety and both user- and patient-friendliness. This success story began in Europe in the 1970s and is now estimated to be worth almost US$140 billion. For the past five years, prefills have been making serious headway in the United States, where the market for prefilled syringes has expanded by 20% each year over the past five years. According to a 2006 IMS report, the prefilled syringe market had already reached more than $18 billion in North America alone (**1**). Globally, volumes of the prefilled syringes have reached 1.2 billion units.

The Prefilling Advantage

Prefilling permits above all exact, safe, and easy administration of a drug. It has also become part of the autoinjection segment of the drug delivery market, which requires prefilled cartridges. An administrator — be that a doctor, nurse, or paramedic — needs only to release air and inject a drug without having to measure out exact dosing. For customers, prefilling pays off in saved bulk substance because vials used for standard injections usually have to be overfilled. Sealing the containers allows for new and ingenious packaging methods and precise tracking systems to prevent mix-ups, tampering, and errors that could threaten the integrity of a drug between filling line and patient. Furthermore, substances can be lyophilized, by which even highly sensitive active substances can be preserved, and packaged in dual-chamber syringes or cartridges, making administration simple.

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The flexibility and safety of the prefills is very much in line with the trend toward home health care. Changing demographics — e.g., an aging population — are fueling the trend, along with efforts by insurance companies to lower health-care costs. Patients with chronic conditions represent a new class of parenteral drug users who have spawned a plethora of user-friendly syringes and injection devices such as pen-type autoinjectors, which use cartridges. There is also a symbiotic relationship between this trend and the pharmaceutical industry, which has been making great strides in the technology of aseptic filling over the past 20 years. Pen autoinjectors for multiple-dose delivery of drugs began their rise in the mid-1980s as devices to carry out hormone replacement therapies for conditions such as diabetes and osteoporosis as well as in fertility treatments.

Long-Term Stability

The challenge in using prefilled systems is for companies doing the filling: Aseptic filling is a complex process that must be carried out with great care in a highly controlled microbiological environment. Therefore, extensive quality control and validation activities for all materials are crucial for the success of a product. With prefilled systems, drugs are in contact with syringe and plunger for up to three years. So the interaction between a drug and its packing components must be tested for leachables and extractables (contaminants that can, respectively,

transfer from the packaging device or can be extracted from it). Regulatory authorities demand special tests such as those encapsulated in the FDA guideline on container–closure systems for human drugs and biologics (**2**). Experienced manufacturers include extractable and leachable testing in the design of their packaging at an early phase in drug development.

User Perspective

Important prefilled application systems are used in treatment of chronic diseases such as autoimmune disorders (e.g., lupus and rheumatoid arthritis). Other growth areas in the prefilled syringe market are reproductive health, antivirals (e.g. interferons, immunostimulants), growth hormones, and vaccines. Such treatments can be administered by regular injection, of course. Traditional syringes filled from vials immediately before administration will always be part of the medical profession because they offer complete dosing flexibility.

On the other hand, prefilled systems meet definite needs and challenges faced by health-care professionals. One of the most obvious is where standard syringes occasionally fail: Dosing errors can have dire consequences. Prefilled syringes contain the exact amount of deliverable substance, so all administrating personnel have to do is select the right one. Because of improved labeling practices, prefilled systems also can reduce medication errors, enabling greater concentration on patients' health rather than label-checking.

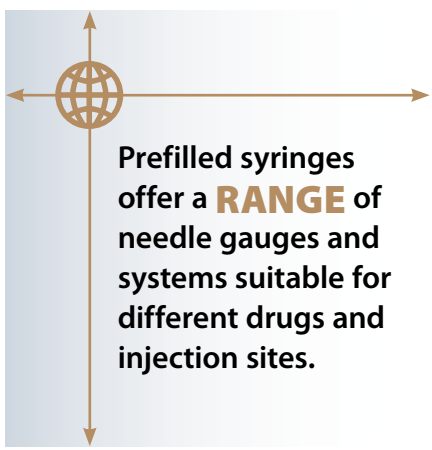
Another concern for health-care professionals is microbial contamination due to manipulation of drug products in hospital or home environments. Because prefilled systems are sealed and checked at their manufacturing facility, where great care is taken to maintain a sterile environment, they also offer far lower risk of contamination. In addition, highly effective methods have been developed to insure against any tampering with these products, so patients can rest assured that the drug in that sealed container is what its label says it is.

Eye on the Needle

Prefilled syringes offer a range of needle gauges and systems suitable for different drugs and injection sites. One particular problem they reduce is the danger of needle-sticks, which generates huge costs annually in laboratory testing and postexposure prophylaxis, for example. Costs in the United States are in the billions. Consequently, many new prefilled syringes come equipped with a needle-safety device. In 2000, the US Congress passed the Needle Stick Safety and Prevention Act, boosting sales of these needle-safety devices. Home use of syringes has also generated interest in various safety methods for prefilled syringes. The new legislation drove pharmaceutical companies to commercialize engineered sharps industry protection (ESIP) systems for their prefilled syringes. Needle-stick injuries are not restricted to health-care professionals or those who administer drugs. Poor disposal of needles puts a large number of others at risk, from plumbers and launderers to municipal workers involved in garbage disposal and even the general public.

Patient Perspective

Drug companies are always working to create the safest and most effective medications that will satisfy health-care needs in the world at large. They are also quite aware of the need for efficient and patient- or user-friendly delivery systems. Formerly, many patients with chronic diseases had to receive sometimes painful injections in hospitals or the doctors' offices. Now, patients are beginning to take a more active role in their own health care and have become more likely to self-administer their own medications at home. The prefilled cartridge used in an auto-injector, for example, is obviously an excellent choice in such a case. Even complex, lyophilized substances can be used in a home setting because the market offers dual-chamber prefilled syringes and cartridges designed to facilitate the reconstitution and delivery of lyophilized drugs. A patient simply breaks a seal, reconstitutes the medication, and then injects it using a syringe or other device, such as a pen injector.



Cost Benefits

Prefilled application systems have several financial advantages over the traditional syringe–vial system. To begin with, on the manufacturing side, prefills require no overfill, so the often costly active substance is used more efficiently. Administrating personnel need not dispose of "leftover" medication — which in itself is an expense. Furthermore, because fewer steps are needed to prepare a syringe — or the dosage on an autoinjector equipped with a cartridge — users can inject drugs much faster than with traditional systems. Storage and disposal are also easier.

Manufacturer Perspective

For drug companies, prefilled systems present a viable option in extending product life-cycles. One challenge parenteral drug makers face is transport and storage of more sensitive drugs. Changes and formulation improvements usually address such problems, but an evolution to new, user-friendly application systems can play a crucial role in increasing the market value of some drugs.

In some cases, this life cycle management method can be planned into drug marketing strategies. If a drug is sure to be a hit and needs to

Photo 1: Dual-chamber syringe
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get onto the market quickly, it can be packaged in a traditional vial. In a subsequent step — once the drug has become established on the market — the company can repackage that drug using prefilled syringes and cartridges or (in case of highly sensitive active substances) offer it in lyophilized form. Additionally, a range of customizing features can be added to meet end-user needs, which can potentially effect product differentiation and market share expansion: e.g., the auto-injector with a cartridge for use by patients at home. Such systems allow exact dosing and control by medical professionals.

A Lively Market

There are few potential blockbuster drugs in the pipelines these days. The pharmaceutical market is diverse and lively as new products emerge, including vaccines, blood stimulants, therapeutic proteins, and interferons. The manufacturing cost of biologics such as recombinant proteins has sparked interest in prefilled application systems to keep prices in check and reduce waste. This is beneficial for manufacturers of a product that may be in short supply, such as some vaccines (e.g., for influenza). This same selling point also holds true for manufacturers of products that are extremely expensive to make.

As for prefilling itself, it is best performed by a contract manufacturer with the experience, know-how, and special facilities to do so. Some pharmaceutical and biotechnology companies lack the resources to do such work in sufficient quantity. Additionally, it is more efficient to outsource the fill–finish phase of a drug to a reliable company that is specialized in prefilling syringes and cartridges — or even vials. An additional benefit is the ability of each drug company to then focus its efforts on further research and development and on drug marketing.

Prefilled System Designs

Aseptic prefilling of drugs has evolved over the years with new materials and improved design concepts. Needles themselves have often been rethought as well as the use of glass or plastic cylinders, and plunger design. In short, almost all aspects are continuously being subjected to optimization. Lyophilizing a drug substance has added an additional factor and given rise to a dual-chamber syringe developed by German contract services provider Vetter Pharma-Fertigung to ease reconstitution for lyophilized formulations.

The dual-chamber system (seen in Photo 1) uses a glass-barreled syringe with a stopper in the middle to serve as a barrier between the two chambers. The drug formulation is lyophilized inside the syringe itself, and the chamber is sealed while the syringes are still in the freeze-dryer. Diluent is then filled into the second chamber, and another stopper is added. On the distal portion is a screw-tapered plunger rod that goes through the finger rest. As a user activates the plunger, it puts pressure on that diluent. The diluent then moves a center stopper, which allows it to escape through a bypass into the front chamber and reconstitute the freeze-dried product.

The dual-chamber syringe allows for fast drug delivery, which can be beneficial for example during emergency situations, such as when a patient experiences a heart attack. The system has been applied to cartridges as well, which means that even home-care patients can use complex formulations without necessarily having to see a doctor for every injection. Dual-chamber and single-chamber cartridges or syringes are used in autoinjectors, needle-free injectors, prefilled disposable needle-free syringes, disposable infusion pumps, and dry powder injectors.

A Viable Option

Prefilled syringes did not appear by accident, but rather as a direct response to the drug delivery concerns of health-care professionals. All 45 physicians who participated in a 2003 study indicated that they preferred prefilled syringes, barring any differences in cost (**3**). Because prefilled syringes have lower drug overfill requirements than traditional syringes do, doctors and hospitals can save doses and (equally important) contribute to a much more accurate

Providers of Prefill Services and Products

Below are listed some of the major providers of syringe-prefilling services and products:

Althea Technologies, Inc. (San Diego, CA) www.altheatech.com

Baxter Healthcare Corporation (Round Lake, IL) www.baxterbiopharmasolutions.com

BD Medical Pharmaceutical Systems (Le Pont de Claix, France) www.bdpharma.com

Cardinal Health, Alaris Products (Dublin, OH) www.cardinal.com/alaris/index.asp

Hyaluron Contract Manufacturing (Burlington, MA) www.hyaluron.com

Vetter Pharma-Fertigung GmbH & Co. (Ravensburg, Germany) www.vetter-pharma.com

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dosing for their patients. Clearly labeled, prefilled syringes maximize overall safety while minimizing the number of steps required for drug administration, which in turn reduces the chance of delivery-related medication errors.

Pharmaceutical and biotech companies must continually discover better ways to create and deliver drugs. Prefilled application systems are an advantageous way to use active ingredients optimally, to extend product life-cycles, and to increase the value and cost-effectiveness of drug products. With home health care on the rise, patients and their physicians are obviously looking for the kind of convenience and safety offered by prefilled systems.

Naturally, prefilling a syringe or cartridge (in particular with a lyophilized substance) is quite a complex procedure requiring enormous expertise. Some drug companies, in particular smaller biotech companies, simply lack the resources and technical know-how to do such work themselves. But this need not be a barrier to their use because some contract manufacturers specialize in lyophilization and prefilled application systems. A reliable partner can offer a full range of services and a complete portfolio of parenteral solutions. Important, too, are state-of-the-art filling lines equipped, for example, with the restricted-access barrier system, which allows great flexibility and safety. Back-up systems and a good track record with regulatory authorities are also crucial. And finally, a service provider should be able to offer an efficient concept for life-cycle management from the beginning.

Indeed, prefilling represents a major improvement in the quality of health care. And that quality must be present at the start of a drug's life.

References

1 IMS Health Report M16757. IMS Health Inc.: Norwalk, CT, 2006.

2 CBER/CDER. *Guidance for Industry: Container Closure Systems for Packing Human Drugs and Biologics.* US Food and Drug Administration: Rockville, MD, May 1999; www.fda.gov/cder/guidance/1714fnl.htm.

3 BD Prefillable Drug Delivery Systems Preferred By Health Professionals. BD Medical: Franklin Lakes, NJ, 2003; www.bd.com.

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