

# The Market Need for Reconstitution Systems

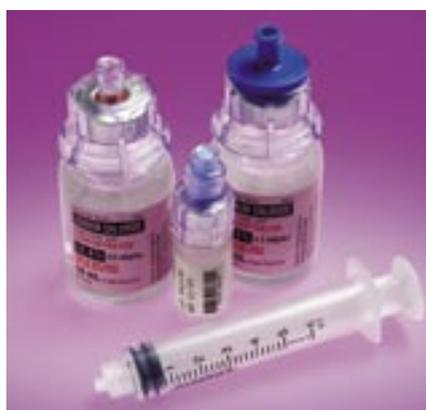
by Graham Reynolds

As the number of lyophilized (freeze-dried) drug products on the market and in development increases, so too does the need for systems and devices to administer them. Many new therapeutics, especially those developed by biopharmaceutical companies, are initially marketed in lyophilized form. A lyophilized drug maintains its potency over time, with extended shelf-life for prolonged storage. Some freeze-dried products may eventually be available as liquids, but lyophilization provides the fastest route to market for many of them — and it is the only option for those unstable in a liquid form.

Lyophilized products require an additional preparation step before administration. This process, known as reconstitution, entails mixing a dry drug product with a liquid to create an injectable solution.

Because many such drugs are used to treat chronic conditions, the number of patients who have to administer a drug themselves or rely on a nonhealthcare professional is increasing. The reconstitution process can be complex and may put a patient or caregiver at risk for accidental needle sticks, inadvertent exposure from spray-back, inaccurate dosing, and noncompliance with a dosing regimen.

Traditional reconstitution requires two vials (one of the lyophilized drug and one of a diluent), a disposable syringe, and two needles. It also requires training and experience. Further, a patient may be at risk of an



**TOP: Needleless transfer devices enable rapid transfer of a diluent into vacuum powder vials; BOTTOM: Vial adapters are a cost-effective way to reconstitute drugs between vials.** WEST PHARMACEUTICAL SERVICES ([WWW.WESTPHARMA.COM](http://WWW.WESTPHARMA.COM))

under- or overdose because the diluent may not be measured precisely. What's more, pharmaceutical manufacturers usually overfill vials by as much as 35% to ensure a sufficient quantity of a reconstituted drug for a correct dose. The overfill compensates for the inherent variability of the manual process as well as the difficulty of removing liquid completely from a vial.

## OPTIONS FOR DRUG RECONSTITUTION

A number of products on the market can provide both professionals and nonprofessionals with safe, convenient, and easy-to-use systems for reconstituting and administering injectable formulations. These systems are provided either as total packaged solutions or as components for specialized use (see the "Other Examples" box).

Many new reconstitution systems can be adapted to currently marketed drugs without changing manufacturing processes or packaging components such as vials, stoppers, and seals. They are offered as total systems that can be packaged with filled drug vials and reconstitution components. Such systems usually consist of a plastic device that joins a drug vial to a diluent container, which can be a prefilled syringe, vial, or infusion bag. Reconstitution devices can be sterile and fully supported by appropriate regulatory filings. To enhance convenience further, all required reconstitution items can be packaged together in a kit.

Dual-chamber syringes provide a lyophilized drug and diluent in a single unit. Reconstitution is achieved by pushing down on the syringe plunger, forcing the diluent through a channel and into the second chamber, where it mixes with the drug to create a solution. The drug can then be injected using an attached needle or can be transferred through a Luer connection. These systems provide a high level of end-user benefits. Pharmaceutical companies, however,

## OTHER EXAMPLES

In addition to the author's company and products described in this article ([www.westpharma.com/markets/biotechnology.asp](http://www.westpharma.com/markets/biotechnology.asp)), here are few other industry examples of approaches to both reconstitution and prefilled-syringe systems. This is not intended to be an exhaustive list, but to illustrate how similar safety and compliance concerns are being addressed.

Of interest: **BD Medical-Pharmaceutical Systems** conducted a survey of healthcare workers' preferences regarding prefilled syringes (BDPS\_marketing@bd.com). It states that "contributing to this rapid expansion are a variety of market trends: an increasing number of biotech drugs entering the market, a growing market for technology that is easier and more convenient to use (especially for patients), legislation requiring safer technology to protect both healthcare workers and patients, and the rise in conversions from vials to prefillable syringes. These are just a few of the factors expanding the prefill syringe market. Of note, the trend toward home-use products (or self-injectables) is expected to fuel continued growth."

**Baxter's ISOLEX 300i magnetic cell selection system** is designed for hematopoietic reconstitution after myeloablative therapy in patients with CD34 negative tumors. The functionally closed system enables passive depletion of tumor cells from autologous apheresis products ([www.baxter.com/products/oncology/cellular\\_therapy/cell\\_selection\\_home2.html](http://www.baxter.com/products/oncology/cellular_therapy/cell_selection_home2.html)).

**Bayer HealthCare's Kogenate FS recombinant factor VIII hemophilia A treatment** is packaged with the company's **BIO-SET needleless reconstitution system**. The system is designed to involve fewer components for reconstitution, reduce the risk of accidental needlestick injuries during reconstitution, and to be easily portable in its new smaller size.

**Baxa Corporation** ([www.baxa.com](http://www.baxa.com)) has developed a dual purpose needle, designed to prevent environmental contamination that can occur during the process of changing needles. The **CyTwo-Fer needle** has a modified hub design to provide vented access to vials or nonvented access to IV bags, performing the work of two devices. Its 0.2- $\mu$ m vent filter is designed for safe vial reconstitution, aspiration, and subsequent injection of drugs into bags or other IV delivery devices.

A Canadian company, **Duoject Medical Systems Inc.** ([www.duoject.com](http://www.duoject.com)), manufactures **Vari-Vial**, a prefillable syringe and bottomless vial; the Inter-Vial system, a closed system to safely, precisely, and intuitively dissolve or suspend and deliver a lyophilized drug such as a protein or peptide compound; E-Z-Link, a basic vial socket connector with a patented "captured needle" feature to reconstitute a lyophilized drug using any ISO standard prefilled diluent syringe and a traditional pharmaceutical vial; and Smart-Rod, primarily for subcutaneous or intramuscular applications.

—S. Anne Montgomery

may face additional challenges in manufacturing and regulatory requirements because of related changes in their primary containers.

One example of a simple system is **the vial adapter**. Such systems connect a syringe of a diluent (either prefilled or filled from another container such as a vial or ampule) to a vial with a lyophilized or dry powder drug. These provide for quick and safe transfer from vials, allowing convenient, optimal-quantity aspiration. An adapter is snapped to the neck of a vial after a plastic button has been flipped off. A plastic spike pierces the stopper; needles are not used. Reconstituted drug is transferred to a syringe by a Luer connection. Vial adapters come

in a variety of sizes and with venting and inline filter options, as well as the option of an incorporated valve system to allow for maintenance of stability for multidose applications.

Adaptations of vial adapters include systems to connect to other containers such as IV bags and cartridges (for subsequent insertion into a pen system) as well as other administration routes such as nasal and oral.

The following are advantages of those and other advanced reconstitution systems:

- They are easy for a patient to use.
- They help protect against drug spray-back and accidental needle sticks.
- Many provide needleless reconstitution and transfer.

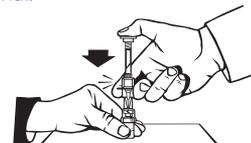
**Figure 1:** Instructions for operating one type of reconstitution system

### Step 1



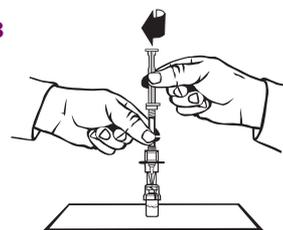
Place the drug vial on a flat surface. Press the connector down firmly on the vial top to seat the vial.

### Step 2



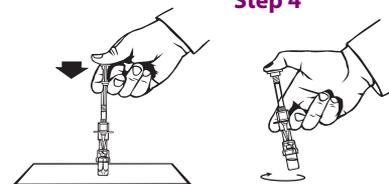
With the drug vial on a flat surface, press down on the barrel of the syringe firmly to fully seat it in the connector. This step places the needle at the correct depth through the rubber stopper.

### Step 3



Screw the plunger rod into the syringe plunger.

### Step 4



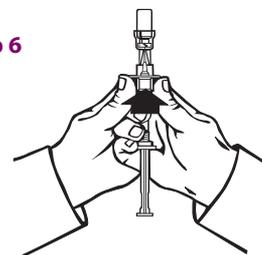
Inject all the diluent into the vial. Grasp the connector and gently rotate the system to rinse the vial sides with diluent and completely mix product and diluent.

### Step 5

Ensure that the syringe is fully seated in the connector. Without touching the connector, grasp the barrel of the syringe, and hold the system vertically (vial end up). Withdraw the reconstituted product into the syringe.



### Step 6



Pull the syringe from the connector by pressuring your thumbs against the plastic tabs of the connector.



**TOP: Mix2Vial® enables fast vial-to-vial transfer; BOTTOM: MixJect I® enables rapid preparation of lyophilized drugs**

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- Because they are convenient, they encourage patients to comply with a dosing regimen, helping to ensure a positive outcome.
- They may help a pharmaceutical company reduce the amount of overfill in drug vials by promoting the use of all of the drug.
- They can reduce problems during the mixing process, such as foaming or incomplete reconstitution of the drug.

### **MARKETED PRODUCTS USING RECONSTITUTION SYSTEMS**

Many marketed products incorporate reconstitution systems, including drugs for the treatment of hemophilia, multiple sclerosis, rheumatoid arthritis, cancer, and hormonal disorders. Many devices are sold in conjunction with drug products; devices are also sold directly to hospitals and clinics.

Reconstitution systems are especially beneficial for products administered in a home setting to treat chronic conditions. Many systems are approved as medical devices by the United States Food and Drug Administration and carry

certification from the Council of Europe for European markets. For the person administering a drug, whether or not a health care professional, advanced reconstitution systems can help promote safe and effective drug delivery and compliance with a dosing regimen.

For pharmaceutical companies, advanced systems can differentiate products in the market. Because the dosing is accurate, manufacturers may be able to reduce the need for drug overfills. The ideal time to evaluate systems for developmental drugs is during phase 2 and phase 3 clinical trials when the effectiveness of the delivery system can be evaluated. For currently marketed lyophilized drugs, systems are available that can be used without the need to change processing and filling lines or packaging components.

Among the criteria used to select an advanced reconstitution system are the type of drug; the diluent volume type; the administration method (subcutaneous, IV, IM); requirements for linking to secondary administration (bag, autoinjector); the competitive environment; speed-to-market needs; and overfill requirements.

The use of an advanced reconstitution system can add value to currently marketed and pipeline drug products. Such systems provide benefits for pharmaceutical companies and for those who administer drugs. They can differentiate products and promote compliance and safety. 🌐

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