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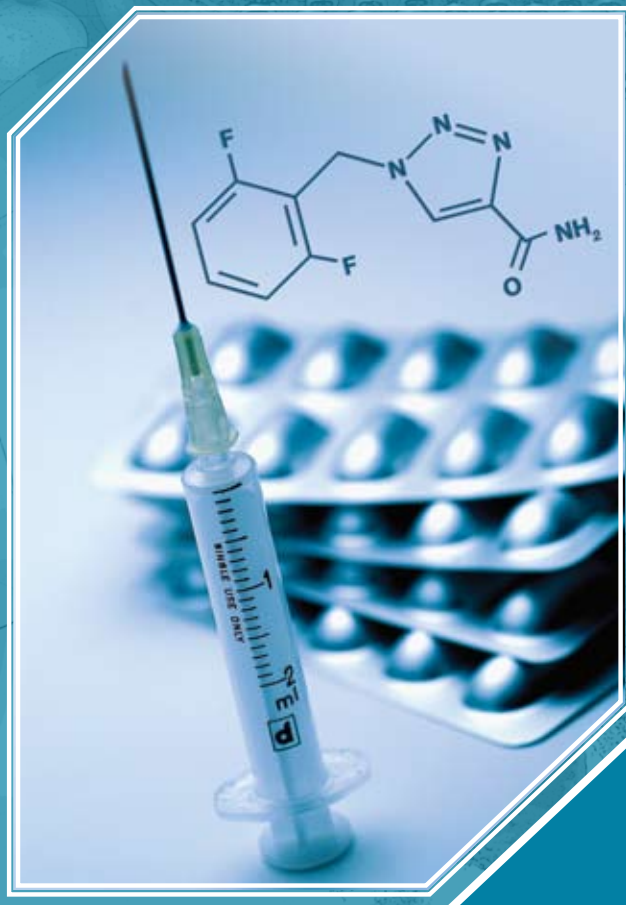
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Moving from Vials to Prefilled Syringes

A Project Manager's Perspective

Raul Soikes



BRAND X PRODUCTS/GETTY IMAGES

Deciding to switch an injectable therapeutic's presentation from a liquid or lyophilized vial to a prefilled syringe requires many financial and strategic considerations. **The author discusses the complex issues involved in making such a change and describes a potential regulatory strategy, including stability protocols and clinical testing, for getting the newly formatted drug to market.**

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Drug development is an arduous, financially risky process that has been estimated to cost pharmaceutical firms an average of \$802 million for each therapeutic gaining marketing approval (1). To maximize return on the initial investment, companies look to strengthen their market position and extend product life cycles through reformulations, new routes of administration, and use of the latest technology.

For injectable therapeutics, one way to accomplish this goal is to move a product's presentation from a vial to a prefilled syringe. A prefilled syringe helps to increase dosing accuracy, convenience, and safety; enhance patient quality of life; and reduce patient time in the clinic. While the introduction of prefilled syringe presentations varies among drug classes and therapeutic categories, the overall market for prefilled syringes is expected to grow by 12.8% per year (see Table 1) (2).

This article presents a project manager's perspective on the rationale and timeline for moving an injectable therapeutic to a prefilled-syringe format. The author also discusses a regulatory strategy that can facilitate a smooth transition to the new dosage form.

Rationale and timeline

The natural first question is, "Why change a drug's presentation to a prefilled syringe?" For many companies, the decision to change to a prefilled-syringe format is strategic because it meets the demands of physicians and patients looking for easier modes of administration and it helps further differentiate the product from competing drugs in the same therapeutic category.

Data from Frost and Sullivan, a global market-research firm, demonstrate the importance of product presentation to physicians and patients. Three of the top five factors influencing a physician's choice of a drug-delivery type—ease of use by patients (16%), convenience (11%), and comfort (9%)—are affected by the presentation of the product. Physicians also commonly view patient satisfaction (14%) and a minimum of side effects (9%) as important factors in their choice of drug-delivery methods (3).

When selecting a drug-delivery device for their patients, 46% of physicians take into account whether it easily enables self-administration (3). Patients who have a choice between drug-

Table I: Partial list of injectable therapeutics and vaccines available in prefilled syringes in the US.

Name (generic)	Therapeutic activity	NDA approval	SNDA for prefilled syringe
Anzemet (dolasetron mesylate) (11)	Antiemetic	Sept. 1997	July 2003
Aranesp (darbepoetin alfa) (11)	Erythropoiesis-stimulating protein	Sept. 2001	Nov. 2007
Avonex (interferon beta-1a) (11)	Antiviral	May 1996	May 2003
Copaxone (glatiramer acetate) (11)	Immuno-modulator	Dec. 1996	Feb. 2002
Enbrel (etanercept) (11)	Tumor-necrosis factor α blocker	Nov. 1998	Feb. 2007
Fluzone (12)	Vaccine for influenza	N/A†	June 2002
Gardasil (13)	Vaccine for human papillomavirus	June 2006	June 2006*
Humira (adalimumab) (11)	Tumor-necrosis-factor α blocker	Dec. 2002	Dec. 2002*
Neupogen (filgrastim) (11)	Granulocyte colony-stimulating factor	Feb. 1991	Dec. 2004
Pegasys (peginterferon alfa-2a) (11)	Antiviral	Oct. 2002	Feb. 2005
Pprevnar (14, 15)	Vaccine for pneumonia	Feb. 2000	Oct. 2008

*Available in prefilled syringe upon approval of new drug application (NDA). SNDA is supplement to an NDA. †New formulation approved each year. Source: *Drugs@FDA*, www.accessdata.fda.gov.

Table II: Differentiation of an injectable therapeutic throughout its life cycle.

Short-term strategy (6–18 months)	Mid-term strategy (18–36 months)	Long-term strategy (> 36 months)
Attach a safety device to a prefilled syringe.	Move from a vial or syringe into an autoinjector or cartridge.	Develop sustained release formulation.
Kit vials with a ready-to-use diluent syringe.	Reformulate lyophilized vials into a liquid vial or prefilled syringe.	Develop alternate route formulation.
Move from a stable liquid vial to a prefilled syringe.		

Source: Adapted from Polen (6).

ceuticals, as well as for producing reformulations or improved delivery devices. Injectable drugs typically are introduced in a vial, because vials enable a faster pathway to regulatory approval, particularly when individual patient dosing varies according to factors such as age or weight.

Once the product is on the market, a reasonable timeline for developing improved packaging depends on whether the initial product presentation is liquid or lyophilized (see Table II) (6). Moving from a liquid vial to a prefilled syringe can be accomplished within 6 to 18 months in most cases.

The timeline is a bit longer for molecules introduced to the market as lyophilized powder. As a consequence, movement to a prefilled syringe from a dry vial typically is considered a mid-term life-cycle strategy. The process of developing a stable liquid formulation and gaining regulatory clearance for the formulation and enhanced packaging may require 18–36 months, and occasionally longer depending on clinical-trial results.

Teva Pharmaceuticals (Petach Tikva, Israel) employed a mid-term strategy in 2002, when it changed the lyophilized vial presentation of Copaxone (glatiramer acetate) into a stable liquid offered in a prefilled syringe. Before reformulation, market share of Copaxone was declining. Yet, the new presentation achieved rapid acceptance in the market; 64% of patients switched to the prefilled syringe version within the first three months of availability. The remainder switched within six months of the new product's launch (6).

The Copaxone prefilled syringe had measurable advantages for patients on chronic therapy for multiple sclerosis, particularly the amount of time required for self-administration. The average time a patient spent preparing for a Copaxone injection was reduced from the 235 s it took to reconstitute the product and draw it into a syringe to 38 s with a prefilled syringe. Consequently, the reformulated version saved a typical patient more than 20 hours over the course of a year. For Teva, increased patient convenience was rewarded with premium pricing, compared with the original formulation. In 2002, the premium started at 5% and rose to 48.6% by 2005 (6).

Similarly, in 2004, Amgen (Thousand Oaks, CA) changed the

delivery devices also judge the ease of self-administration (37%) and whether the product has been recommended by the physician (24%) (4).

Prefilled syringes also present economic advantages for pharmaceutical companies marketing injectable therapeutics. Because the devices meet customer demands for increased safety and convenience, companies often are rewarded with premium pricing for prefilled syringes compared with vials (5). Moreover, prefilled syringes help increase the saleable yield of active pharmaceutical ingredient (API). Filling API in prefilled syringes enables the required dose to be delivered precisely. Consequently, only trace amounts of API remain in the needle of the prefilled syringe after injection. In contrast, single- or multi-use vials require overfilling the API to ensure that an accurate dose is pulled into the syringe each time.

The question of when to move an injectable therapeutic into a new presentation is as significant as the rationale for why. Speed to market is a critical factor for the development of new pharma-

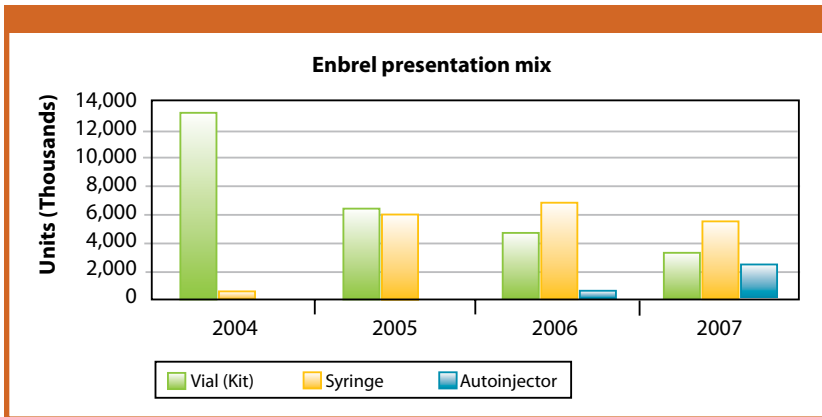


Figure 1: Unit sales of Enbrel following movement from a dry-vial prefilled diluent-syringe kit to a prefilled syringe and autoinjector (5).

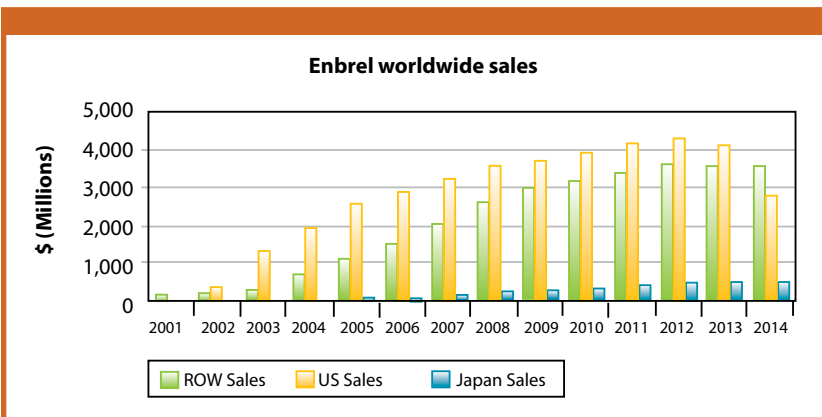


Figure 2: Growth in worldwide and projected sales for Enbrel following introduction of a prefilled syringe and autoinjector format in 2004 and 2007, respectively (5). ROW is rest of world.

presentation of Enbrel (etanercept), a treatment for rheumatoid arthritis, from a dry-vial prefilled diluent-syringe kit to a single-use prefilled syringe. In 2006, the company launched Enbrel in an autoinjector, which further differentiated the product and added value. Although unit sales of Enbrel have remained stable, sales revenue has increased because of the price premium associated with the prefilled syringe and autoinjector formats (see Figures 1, 2) (6).

Regulatory strategy

For most companies, the process of moving an injectable therapeutic to a prefilled syringe can be fairly complex because of sterility and stability issues associated with small and large molecules in addition to challenges related to the size and structure of biologic molecules. To facilitate a smooth path to regulatory approval, companies must establish a strategy that carefully evaluates proposed changes in manufacturing, packaging, and shipping processes and that ensures the company can validate the effect of these changes on the therapeutic molecule.

The US Food and Drug Administration requires that any change in the manufacture of a drug product, whether major or minor, be put into place only after the license holder assesses the

effect of the change on the identity, strength, quality, purity, and potency of the molecule, because these factors will influence the safety and effectiveness of the pharmaceutical (7).

In addition, FDA has stringent requirements for changes that may affect parenteral drug product. These requirements pertain to moving a therapeutic to a prefilled syringe from another container-closure system; silicone treatments in the closure systems such as in elastomeric closures or the syringe barrels; and changes in the size or shape of a container that holds a sterile drug product (8). Any such change is considered to be “major” by FDA and must be documented in a prior approval supplement.

Stability and clinical testing for parenterals depend on a multitude of factors, including the formulation, indication, mode of administration, size and functionality of packaging, and the introduction of new materials. Any potential need for clinical or stability data must be noted and planned for at the outset, and included in the stability protocol.

Getting started. The choice of a syringe system should be a critical part of the regulatory strategy and must be considered at the outset, perhaps even with product reformulation. The syringe system is important because a packaging system that is acceptable for one therapeutic will not necessarily work for another because of differences in dosing ranges, patient populations, and in how individual molecules react to surrounding materials and conditions.

Evaluation of the proposed syringe system must consider these factors, and regulatory submissions must support the suitability of the proposed packaging and storage conditions.

An analysis of proposed syringe systems should take into account their appropriateness, functionality, and materials. First, the dosing device has to be suitable, and its graduations appropriate, for the intended patient population. At a basic level, the syringe must deliver the dose in the amount and rate stipulated in the package insert. In addition, the physical characteristics of the liquid drug formulation must be appropriate for the dosing device to ensure accurate dispersion of the drug through the needle.

Second, the proposed system must function correctly throughout its shelf life. The results of coating integrity testing, effect of viscosity, and syringe-ability must be considered. Moreover, scale intervals on the syringe must represent the labeled dosages, and graduations in dose must be easily read. The type should be embossed or printed and legible throughout the shelf life of the product. These markings cannot fade or become dislocated during the use or life of the product. In addition, stopper movement during use, as well as the effect of shipping on stopper movement,

Table III: Filing requirements for prefilled syringes.

Attribute*	Move from liquid vial	Move from lyophilized vial
Container-closure	Similar? Refer to previous extractable and leachable studies to impart lubricity. Siliconization may be needed.	
Formulation	No change.	Change from freeze-dried powder to liquid.
Storage conditions	No change. A stability study that collects 3 months of comparative accelerated data and long-term data of at least 1 batch (3 may be required). A clinical study is required if degradation or impurities profiles change.	May change. A stability study that collects 3 months of comparative accelerated and long-term data on 3 batches. A clinical study is required if degradation or impurities profiles change.

*Changes in indication and routes of administration requires submission of clinical data to authorities.

must be considered to ensure sterility of the product and to avoid particulate contamination.

Third, materials in the proposed syringe must be compared with those of the current vial. The analysis should consider whether:

- The material in the proposed syringe, including in the container, plunger device, and closure system, protects the drug product
- The syringe system introduces a new material
- The system will require any changes to the drug product formulation.

Choosing a container and closure system made of the same materials as the vial will eliminate the need for additional extractable and leachable studies. Any new materials, including those in the hub or needle, will need to be evaluated in stability testing. Extractable studies also must include proposed labels, adhesive, and ink if the barrel of the syringe is not made of glass.

Stability protocol. FDA rules governing current good manufacturing practice (GMP) stipulate that companies develop and thoroughly document a testing program to assess the stability characteristics of the drug product (9). Consequently, a company must define stability testing requirements related to the container-closure system. These requirements include how temperature, humidity, and light influence the shelf life of the drug and help to determine appropriate storage conditions and expiration dates for the product. A stability protocol that is specific to the molecule and the proposed drug-delivery device must be written, implemented, and evaluated to assess the stability characteristics of the molecule in the container-closure system (9).

Although some extractable and leachable studies related to the dry or liquid vial presentation may be transferable to the new format, some new stability testing is required when mov-

ing an injectable therapeutic to a prefilled syringe (see Table III). The long, narrow dimensions of a syringe increase the molecule-to-surface-area ratio from the previous vial presentation. As a consequence, accelerated and long-term stability studies are necessary to determine whether the change affects the extractable and leachable parameters and to understand the impurity and degradation profile of the molecule in the container-closure system.

The stability protocol should detail the sample size, test intervals, storage conditions, validated analytical methods to be performed, the container-closure system, test specifications, and number of batches required. In addition, reconstitution studies will be required for parenteral products offered in a kit with a prefilled diluent syringe or in a dual-chamber prefilled lyophilized syringe. Tests and specifications must be based on knowledge of the degradation pathway for the particular molecule, use validated and stability-indicating methods, and specify limits appropriately.

Clinical testing. Clinical studies are required when there is a change in indication or new route of administration for the drug. However, movement from a dry or liquid vial to a prefilled syringe also necessitates clinical testing if the reformulated drug's degradation or impurities profile change.

Scenario one: liquid vial to liquid prefilled syringe

A company markets a contrast imaging agent used in the imaging of major organs. Originally available in 50-mL, 100-mL, and 200-mL single-use vials for intravenous and intra-arterial administration, the company seeks to make the product available in 10-mL and 50-mL prefilled syringes for intrathecal administration for imaging the spinal cord and nervous system. The 50-mL syringe also would be used in the previously approved routes of administration and indication.

In this situation, it is important to consider which factors change and which remain the same. The container-closure system are new, meaning a new size and dimension of container and new functionality of the device are involved. Because the device would enable administration directly into the spinal cord, the route of administration is new, as is the indication. The formulation and long-term storage conditions remain the same, however, because the contrast imaging agent was previously available in a liquid vial.

In selecting a syringe system, the company chooses a device with components similar to those used in the single-use vials. Because the glass and rubber formulation are identical between vial and syringe, previous extractable and leachable studies will apply. However, the company must compare all the materials in the container-closure system because some new materials may be introduced in the components. In addition, the syringe may require additional siliconization to improve the function of the plunger.

To support the regulatory filing, the company will need to submit three months of comparative accelerated stability data. Long-term data on at least one batch, possibly three, will be needed at the time of submission. Moreover, the company will need to commit to placing the first of three production batches on long-term stabil-

ity and to placing another batch on long-term stability each year. Additional clinical data also will be needed to support the new indication and the new intrathecal route of administration.

Scenario two: lyophilized vial to prefilled syringe

A company producing a lyophilized product packaged with reconstitution fluid for intramuscular injection considers marketing a prefilled syringe for the same indication, in the management of rheumatoid arthritis. The company must reformulate the molecule to a stable liquid. The route of administration will remain the same.

The container–closure device, however, will change, which means that some materials and the functionality of the system will be different. In addition, long-term storage conditions may change because of the new formulation.

When evaluating a syringe system, the company must choose one with components that are similar to those used in the vial and reconstitution device to best leverage previously conducted extractable and leachable studies. As with other prefilled syringes, additional siliconization may be necessary. Clinical studies will be required as well if the degradation or impurity profile changes.

Upon submission, FDA will require three months of comparative accelerated data and long-term data on three batches of drug product. The stability tests will need to focus on appearance, color, clarity, sterility, pyrogens, syringe functionality, container–closure integrity, impurities, and particulates. The company also will need to commit to placing the first three production batches and annual batches on long-term stability tests.

Conclusion

The process of moving an injectable therapeutic from a vial presentation into a prefilled syringe or, perhaps, into an autoinjector format, can be complex, regardless of whether the original product is in a liquid or lyophilized formulation. Companies pursuing a new dosage form must carefully document the sterility and purity of the product and ensure the stability of the molecule in the new container–closure system. Complexity of the process multiplies when the dosage form is to be marketed on a global scale. Countries differ in the interpretation of regulatory guidelines established through the International Conference on Harmonization (10).

To ensure a smooth and speedy transition to a new dosage form, most companies assign responsibility for the change-management process to a project manager, who coordinates roles and responsibilities of the team involved in the project, establishes processes and procedures, and manages regulatory submission timelines. Working with team members, the project manager develops and implements the regulatory strategy to control and properly validate the effect of new processes and materials on the therapeutic molecule.

The project manager also helps to select and coordinate the efforts of external partners, including research organizations,

suppliers, and manufacturers. The choice of these external partners is critical, particularly for companies with limited experience with multiple regulatory authorities or with the formulation or manufacturing of therapeutic molecules. For example, a contract manufacturing organization with a drug master file on record with FDA for its facilities, processes, or other articles used in the manufacturing, processing, packaging, or storage can help reduce the amount of paperwork that must be submitted. Moreover, in some instances, having a fill–and–finish site that passed inspections within the past year may limit the need for an additional visit by that inspector before regulatory approval.

When working with injectable therapeutics, the fastest and most efficient path to market for a new delivery device is one in which processes are rigorous, documentation is thorough, and team members are experienced and capable. The project manager can facilitate a smooth transition to the new dosage form by developing and carefully implementing the regulatory strategy and by choosing qualified, effective partners.

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