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Switching delivery formats: A lifecycle management strategy for sterile injectables

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Executive summary

Changing delivery formats for sterile injectable therapies can be a valuable strategy for effectively managing the lifecycle of a drug. Depending on the specific circumstances, switching formats can help bring a drug to market more quickly, make a drug usable in more situations, provide cost efficiencies for the supplier, and ease medication administration to patients.

For example, a growing number of suppliers of biologics are moving their products from bulk glass vials to prefilled syringes due to the ease of use and convenience syringes offer, as well as their ability to eliminate dosing errors and, thus, improve patient safety. With a prefilled syringe, medications can be delivered directly and immediately to the patient, whereas vials require multiple steps prior to injection—flipping the dust cover, cleaning the stopper surface, prepping a syringe, withdrawing the medication, and checking the dose in the syringe—all of which take extra time and introduce opportunity for error.

Several factors must be considered before switching delivery formats, however. These include technical considerations, process and cost implications, supply chain requirements, regulatory requirements, and lead times. A successful transition also requires a thorough understanding of the physicochemical properties of the molecule, the potential interactions with device components, and the impact of formulation and process variables on product stability and quality.

This report provides insight into the benefits and challenges of transferring a therapeutic compound from one injectable format to another, focusing specifically on the following:

- The material and process information and data needed to inform decision-making
- The technical and analytical requirements for ensuring product integrity
- The regulatory and timeline considerations for commercializing the product

Introduction

The injectable drug market, which is one of the fastest growing segments in the pharmaceutical space, is expected to reach $510.3 billion in 2022, with a CAGR of 7.88% over the forecast period.[1] The increasing preference for large molecule drugs, the worldwide demand for the COVID-19 vaccine, and the increasing number of chronic diseases, including cardiovascular disorders, diabetes, and cancer, are fueling the growth.

With the market growth, there is a corresponding increase in demand for the various types of primary packaging used to deliver sterile injectable products to market. As a result, supplies are tightening and prices are rising, leading suppliers of injectable therapies to consider changing delivery formats. In addition, as more biologics go off-patent in the next three to four years, the demand for generics and biosimilar injectables is expected to grow, creating still more pressure on suppliers to reevaluate their drug's delivery format.

In addition to supply and cost, considerations related to product storage, quality, convenience, ease of administration, and patient preference may play a role in the decision to switch delivery formats. From a business perspective, a delivery format change can help differentiate a product from competing drugs targeting the same therapeutic indication and can potentially extend patent production.

Common presentation shifts

There are multiple options for sterile injectable primary packaging. Among the most common are ampoules, liquid filled vials, lyophilized vials, prefilled syringes, prefilled cartridges, and dual-chamber prefilled syringes and cartridges.

One fairly common delivery format change is the switch from a frozen liquid vial to a liquid vial stored at 2°C to 8°C. The incentive for making this change is the high cost of storing and distributing a drug in a frozen state. However, many products start out in a frozen liquid vial for the sake of stability. Drug substances, especially in the case of biologics, are typically held at –70°C unless and until there is enough data to support a move to a refrigerated liquid storage format. Because it takes time to gather that data, products commonly begin their lifecycle in a frozen liquid bottle to get them into the clinic trial stage as quickly as possible.

In addition to supply and cost, considerations related to product storage, quality, convenience, ease of administration, and patient preference may play a role in the decision to switch delivery formats.

When drug products developed in liquid or frozen form need to be shipped to locations where refrigeration is not readily available, or when the products need to be stockpiled for a long period of time, it may make sense to transition from a refrigerated liquid to a freeze-dried (lyophilized) formulation. Freeze-drying has become one of the most important processes for the preservation of biological products in particular.[2] The process entails crystallizing the product at low temperatures followed by sublimation directly into the vapor phase.

The increasing prevalence of complex APIs and biologics has resulted in more pharmaceutical and biotech manufacturers turning to lyophilization to address formulation stability challenges, but lyophilization is a complex and prolonged process that requires optimization of process and formulation variables.[3]

An increasingly prevalent format change is the move from liquid vials to prefilled syringes. In fact, prefilled syringes are one of the fastest-growing classes of drug delivery device due to advances in technology and increased development in parenteral drugs.[4] Topping the list of reasons for moving a drug that is currently delivered in vial form

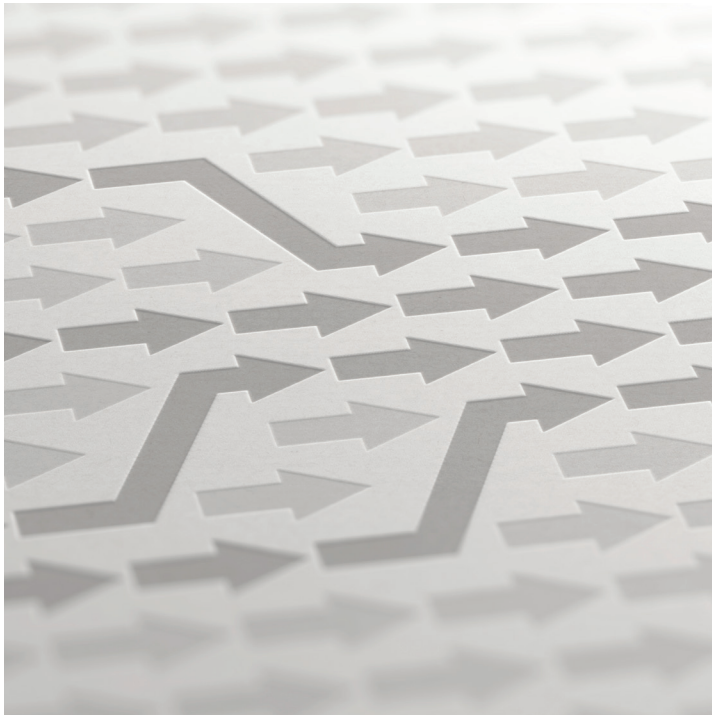
into a prefilled syringe are convenience, ease of use, patient safety, and patient preference. The conversion also improves dosing control, minimizes waste, and enables developers to extend their drug's patent, helping them manage the brand lifecycle of their product.

Moving a product from vial to prefilled syringe can also be cost and resource efficient when dealing with a drug substance that is extremely rare or of extremely high value, as it can help conserve the product. Prefilled syringes can also be useful when the typical dosages for the drug are very low—possibly as low as 50 µL. Syringe filling lines can sometimes fill less volume than a vial. Until recently, a 2R vial, which holds 3 mL, was the smallest vial on the market. So, if a product had a dosage of only 50 µL, approximately 0.3 mL would have to be put in the vial because that's the capability of the line. There would have to be that much product in order to be able to see it and withdraw it. In contrast, syringe filling lines can get down to 0.2 or maybe even 0.15 mL, enabling higher yields of filled units per batch of drug substance.

Finally, moving to a prefilled syringe can be useful for products that have breakthrough or fast-track designation from the FDA. When clinical timelines are compressed, the earlier the transition to a syringe, the sooner the stability data needed for regulatory approval and commercialization can be collected.

Key considerations for changing delivery formats

With few exceptions, most drug products begin their development lifecycle in a bulk glass vial, as it is a relatively simple and inexpensive format that allows a product to get to clinical trials more quickly. Vials are also often the better delivery format at the beginning of a drug product's lifecycle, when dosing flexibility is required, such as during early treatment phases when the optimal dose or concentration has yet to be determined or during dose-escalation studies. But during the four-year clinical trial pathway toward commercialization, it often makes sense to move a drug to a different delivery format. The ultimate goal is to ensure that the product can enter the market using the delivery format that best serves the needs of patients, providers, and the marketplace.



Making the move: A migration road map

Successfully migrating a drug product from one delivery format to another is a complex multidisciplinary undertaking that requires collaboration across product development, quality, engineering, manufacturing, supply chain, and regulatory teams. Among the factors that need to be considered for determining the optimal format are the molecule type, the value of the product, long-term storage goals, sensitivities and technical considerations, timeline, regulatory path, route of administration, and place of administration. Some of the critical considerations are described in the following sections.

Material matters

When a product is being converted from one delivery format to another, the physiochemical properties of the compound must be closely monitored to ensure that the quality is not compromised by environmental contacts or any aspect of the manufacturing process. For example, a switch from a frozen liquid to a 5° C liquid or freeze-dried product will require the evaluation of excipients such as cryoprotectants and bulking agents to determine whether these materials have any effect on the integrity of the product.

When moving from a vial to a syringe, developers need to screen all the component parts to ensure that no adverse effects arise from the physical contact between the product and any part of the syringe. For example, glass syringes are typically made using silicone oil that's either sprayed or baked on, and staked needles have a tungsten spike. To be sure a product will tolerate contact with those elements, syringes must be filled with the product in a non-GMP setting, and stability and compatibility studies must be conducted, using a vial as the control and potentially other elastomers as well. During this testing process, a variety of different variables must be considered, such as the use of plastic versus glass syringes and the benefits and drawbacks of different types of stoppers.

In addition to these physical tests, functional tests, such as break loose and glide force tests, are also needed. Though these types of tests do not have to be conducted with a vial, they are essential for syringes as they are vital for proving the plunger will be able to effectively force the product out of the syringe. For biologics, shear testing is also critical. For example, if a small, 29-gauge needle is used with a highly concentrated biologic at 150 to 200 mg per mL, shear testing is needed to determine whether there will be any negative effects on the chemical compatibility or chemical stability of the product when it is forced through the needle.

Timeline considerations

Determining when to move an injectable therapeutic into a new presentation is a strategic consideration. Just as speed to market is a critical factor for the development of new therapeutics and reformulations, it is also important for improved delivery devices. As noted above, sterile injectable drugs are typically introduced in a vial because vials enable a faster pathway to regulatory approval, especially when there is variation in individual patient dosing. 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.

Regardless of whether it's a change in a vial dimension, a move to a new manufacturer, a move from a bulk vial to a ready-to-use vial, or a move from a vial to a syringe, every alteration triggers regulatory considerations.

Much of the timeline is taken up by the stability and compatibility tests, which are typically conducted on two to three different types of syringes. It takes six to 12 months for these results to become available. This time frame is important to keep in mind, as it has a direct impact on how soon syringe components can be ordered. A good goal is to have a product in its final presentation for commercialization by phase 3. This means bridging studies should begin during phase 2 so that by late phase 3 or by PPQ, the product can go into the syringe in time for commercial launch.

Regulatory considerations

To facilitate a smooth path to regulatory approval, drug sponsors must develop a comprehensive strategy that accounts for and documents all planned changes in manufacturing, packaging, and shipping processes and provides the necessary data to show the effects of these changes on the drug product.

For example, there are specific requirements related to a product's move from a glass vial to a plastic vial. These requirements include extractable studies, container closure integrity testing (CCIT), Class VI plastics compliance, and BSE/TSE statements. Of these, CCIT is particularly important, as it ensures that the product can maintain sterility with the new components, which is the number one concern when dealing with sterile products. These and additional requirements are described in Figure 1. Regardless of whether it's a change in a vial dimension, a move to a new manufacturer, a move from a bulk vial to a ready-to-use vial, or a move from a vial to a syringe, every alteration triggers regulatory considerations.

Figure 1

Type of Change	Requirement
Glass to new material (e.g. plastic)	Material characteristics for leach/extract studies; finish evaluation for CCIT; Class VI plastics compliance; BSE/TSE
Change to different composition or type of glass	Assess the glass characteristics in line with USP<1660> to determine delamination risk (lyo less critical compared to liquids) Hydrolytic resistance to be assessed. Stability is not avoidable
Change in vial dimensions	Machinability and CCI studies
Changes in vial sterilization or depyrogenation method (e.g., changing from moist to dry heat)	Only for RTU supplied article: assess the validation of sterilization/depyrogenation of the Site (make sure the qualification of process is available)
Change in stopper rubber/elastomer material	Stability studies supporting the compatibility. Extractables/ leachables. Assess residual moisture for lyo products. Machinability trials and CCIT
Changes in how the stopper is supplied (e.g., unprocessed, RTS, and RTU)	Validation package for the supplier process. Assessment of in-house steam sterilization cycles and pre-sterilization handling route

Conclusion

The decision to switch an injectable therapeutic from one delivery format to another may be driven by quality requirements to preserve product safety or potency, the desire to develop more patient-centric administration formats, or the need to create more convenient products. Often, the decision is made as part of a lifecycle extension strategy.

In all scenarios, the transfer itself is a complex, multistep process requiring substantial resource investment, careful planning, and close collaboration across quality, engineering, validation, procurement, and regulatory teams.

In addition to the investigation and documentation of product sterility and purity, the stability of the molecule in the new container and closure system must be analyzed and documented. The testing period must be figured into the timeline to ensure that sufficient amounts of the correct materials are procured by the time they will be needed. Additionally, all project stakeholders should have a clear understanding, as early in the process as possible, of the regulatory requirements of all the countries in which the product will be marketed to ensure that there are no compliance obstacles.

When carefully planned and closely managed, switching delivery formats for sterile injectable therapeutics can be an effective product lifecycle management strategy that not only improves the return on a company's development investment, but also benefits patients and providers.

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