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Challenges And Practical Solutions For Switching To Prefilled Syringes For Injectables

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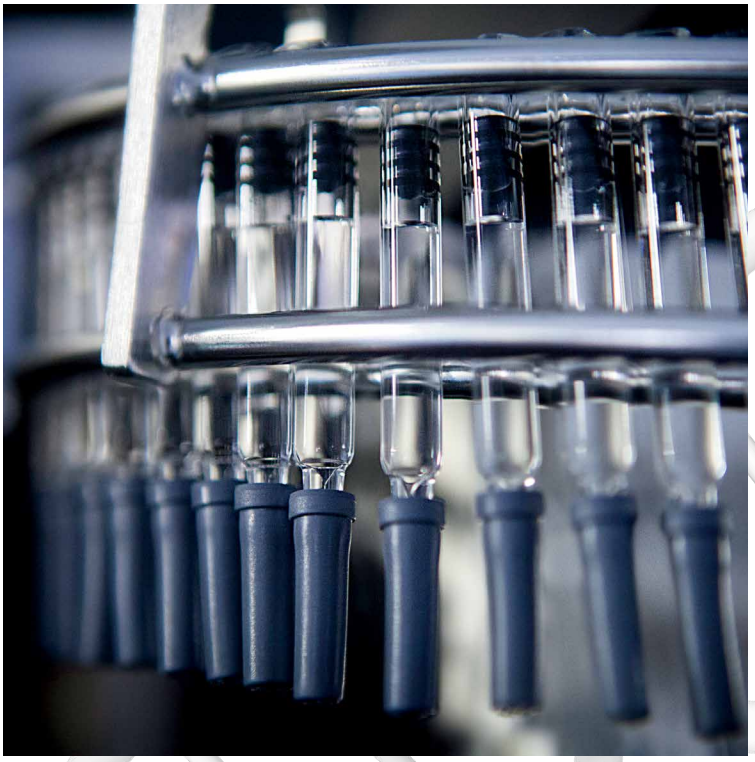

The sterile injectables market is seeing a consistent increase in demand driven by the underlying growth of biological therapies, as shown in Figure 1.

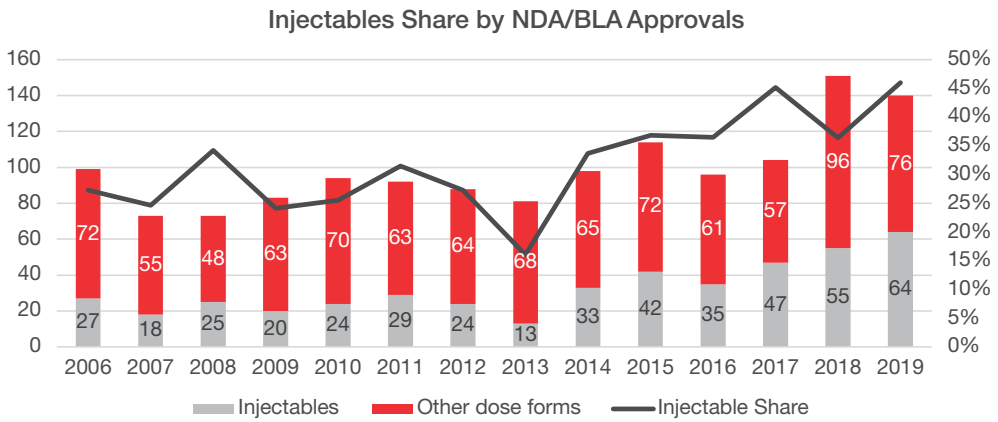

Figure 1: Share of injectable drugs in new drug application (NDA)/biologic drug application (BLA) approvals (Source: CDER and CBER Approvals - PharmSource Injectables Report and FDA website)

There are several end-product formats companies can choose from when developing sterile injectable drugs. The most common ones are liquid or lyophilized vials, prefilled syringes, and cartridges. Due to an increase in self-administration of injectable drugs, the market of drug products in prefilled syringes is expected to reach $9.53 billion by 2026. Some of the critical patient benefit and improved outcomes prefilled syringes offer include:

- Can be administered quickly, which is a key benefit in critical patient situations
- Able to self-administer treatments at home for chronic diseases without the need for hospitalization[3]
- Reduced risk of contamination (no reconstitution is needed before the injection and this prevents both microbial and chemical cross contamination)
- Minimized risk of injuries with physicians, as minor handling is required

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- Improved dosing accuracy (filling volume is accurately set to deliver the desired dose with no need of overfill)
- Reduced costs, especially for expensive biologics, as only trace amounts of API remain in the needle of the prefilled syringe after injection, which increases the overall yield of the manufacturing process

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It is not uncommon for companies that launch commercial drug products in the prefilled syringe format to do so after initially using other product formats, such as vials for the development and clinical trial phases, as overfilling is commonly requested. However, the development of an injectable drug-device combination, such as a prefilled syringe, is a complex process that requires substantial investment of resources to achieve desired and successful outcomes.

The best time to switch from the initial vial format to the commercial presentation is likely before Phase III clinical trials, as most of the critical development activities have been already accomplished and the final formulation is set. This includes the drug substance synthesis, selection of administration method (subcutaneous. vs. infusion), and the establishment of the clinical dosing pattern.

A scientifically robust bridging strategy linking the initial vial presentation used in early stage clinical trials to the commercial one is required to safely introduce these changes into the clinic. The parameters for setting up an adequate bridging package depends on the level of risk associated with the changes.

For example, when the formulation is the reason for switching from lyo powder presentation to liquid formulation in prefilled syringes, then there must be evidence of efficacy for the same dosing regimen and route of administration, and indications. This relies on the demonstration of bioequivalence of the new liquid formulation compared to the lyophilized powder and needs to be supported by the similarity of the pharmacodynamic endpoints. As novel excipients are introduced and the surface of contact increases, additional extractable and leachables studies must be conducted to minimize any safety concerns linked to the formulation change.

Expertise about how primary packaging can impact the overall quality of the product is beneficial when planning the steps that must be taken to meet this crucial milestone in the overall lifecycle of a product.

The table below outlines the effects primary packaging can have on product quality:

Test/specification	Effect of primary packaging
Assay	Adsorption issue, pH change, photostability, oxidation
pH	pH change
Sterility	For multiple doses
Endotoxins/pyrogens	Leaching of plastic components from sterile bags, rubber closures
Particulate matter	Precipitation, induction of crystallization, aggregates formation, leachables
Antimicrobial preservative content	Adsorption or inactivation due to oxidation
Antioxidant preservative contents	Permeability to oxygen, heavy metal leaching in vials
Extractables and leachables	Different dosage forms
Functionality of delivery systems	Syringeability, gliding, and break-loose force
Particle size distribution	Induced crystallization or aggregation
Redispersability	Shape of primary packaging

Figure 2: Effect of primary packaging on different specifications used for injectables[2]

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How to select the most appropriate prefilled syringe

Once a decision has been made to use prefilled syringes as the commercial product format, the next step is to select what type of prefilled syringe best meets delivery, logistical, and economic criteria for better positioning on the market. This should be based on the target product profile and the market where the product will be positioned.

In addition, extensive studies about potential interactions that can arise from the drug product constituents and contact parts present in the prefilled syringe should be taken in consideration. As depicted in Figure 3 below, prefilled syringes are complex multi-component products with multiple points that need to be evaluated to safely adapt a drug product to a prefilled syringe:

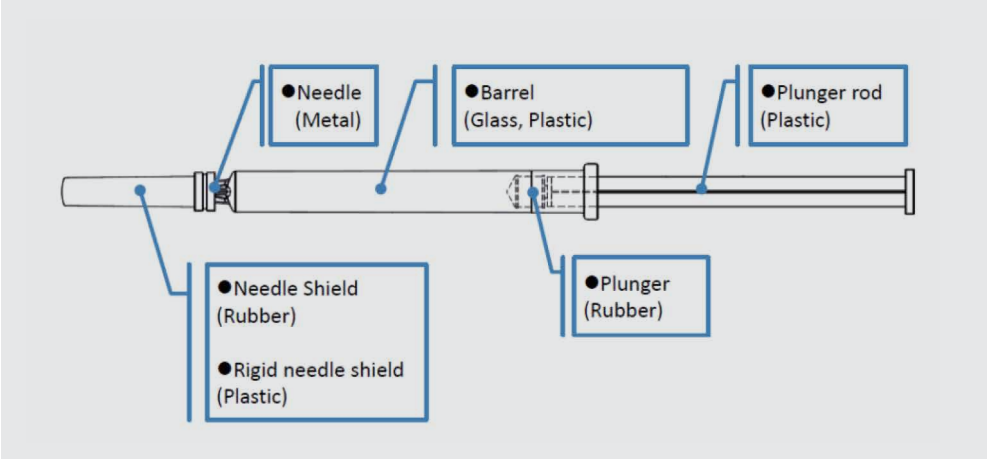

Figure 3: Multiple contact parts content in a prefilled syringe.

These interactions need to be carefully investigated to prevent any potential incompatibilities with the product specifically for biologics. In addition, prefilled syringe systems have to meet various requirements and functionalities, such as container closure integrity, heat resistance, shock resistance, and plunger gliding. An adequate development process must also support the suitability of the proposed new packaging and storage conditions.

Staked needle versus Luer Cone/Luer Lock syringes

Currently, there are two types of syringes available on the market; staked needle syringes in which the needle is already pre-attached, and the Luer Cone/Luer Lock syringes to which the user attaches a hypodermic needle at the time of injection. Both types of syringes are described in detail in the ISO 11040-4 Standard. Luer Cone/Luer Lock syringes offer the patient the advantage of selecting a needle based on where on their body they will be injecting it. The table below outlines the various needle sizes available.

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Type of injection	Needle diameter (gauge)	Needle diameter (mm OD)	Needlelength (inch)	Needle injection angle
Intradermal (ID)	25-27	0.5-0.4	3/8-5/8	5º-15 º
Subcutaneous (SC)	23-30	0.6-0.3	3/8-5/8	45º-90 º
Intramuscular (IM)	18-25	1.2-0.5	5/8-1.5	90 º

Table 1: Typical needle geometries for common routes of administration[4]

The use of an incorrect needle size can lead to a misplaced deposit of the drug, while an error during assembly can create leakage that results in inaccurate dosing. The staked (or pre-attached) needle syringe has emerged as an effective option to minimize these risks, particularly with certain types of drugs, such as heparins, some vaccines, and biologics.

While staked needle syringes offer potential advantages for the dosing of patients, their use does raise additional considerations for the stability and potentially, safety, of the drug product formulation. This is a consequence of their method of manufacture.

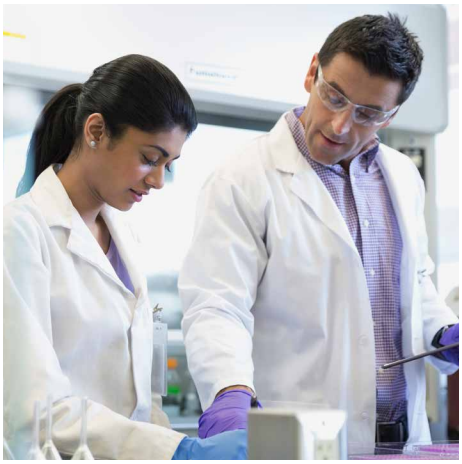
The manufacturing process for stacked needle is as follows:

1. Syringes are formed using glass tubes molded by flames.
2. The needle is applied to the tip with a tungsten pin and then bonded with a UV cured glue.
3. Syringes are washed, and the barrel is siliconized. This can be done only after needle insertion, as this process can interfere with glue and needle application.
4. A soft or rigid needle shield is applied.
5. The syringe is nested, tubbed, bagged, and then sterilized (usually through ethylene oxide treatment).

Because this process is significantly complicated and costly, there is a limited possibility to choose a large variety of needle gauge and length. The complexity of prefilled syringe systems also means many aspects need to be considered in order to anticipate potential incompatibilities between syringe components and the drug product.

The pin used to create the tip for needle insertion is made from tungsten, which is a heavy metal, with chelating and oxidative properties. Even if the residual trace amount in the syringe is not a safety concern, it can catalyze degradation pathways for biologic molecules, as it is known that protein aggregation and oxidation are induced by minimal amount of this metal. The UV-cured glue used to bond the needle to the glass tip and/or its residuals also introduces the risk of leaching into the solution and interacting with drug product.

The amount of silicone oil used for barrel lubrication and to allow the gliding of the plunger is another point of investigation during prefilled syringe scouting. The silicone is applied by spraying silicone oil onto the glass or by coating the glass with a silicone emulsion that is baked onto the glass. The main goal for prefilled



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syringe suppliers is to lower the amount of silicone oil, in order to minimize the risk of interaction with biologics as this can cause particulate formation. Nonetheless, even at lower levels, silicone can interact with proteins and lead to aggregation, or silicone can be detected as particulates during particle testing. One option for minimizing the amount of free silicone oil is thermal fixation of the silicone oil on the glass surface in a process called baked-on siliconization.

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Recently, prefilled syringe suppliers have developed polymer-based prefilled syringes. Compared to glass, these syringes can provide important advantages, such as a higher break resistance, low leachable profiles from heavy metals, and the elimination of glue and tungsten, which prevents protein aggregation as the needle is inserted by molding. The table below summarizes potential degradative interactions between the drug product formulation and syringe materials.

Phenomenon	Causing factor	Related material
Physical	Aggregation by silicon oil	Independent of material
	Aggregation by tungsten	Glass
	Interaction with glue	Dependent on manufacture
	Excessive shaking	Independent of material
Chemical	Alkali elution	Glass
	Gas permeability	Polymer
	Residual radicals	Dependent on sterilisation

Table 2: Potential interactions between drug products and prefilled syringes material

Auto injectors

Another consideration when looking at prefilled syringes is whether auto injectors should be selected as the delivery mechanism for drug administration. Auto injectors automatically insert the needle and perform the injection process while ensuring that the prescribed dose of medication is delivered in full.

Auto injectors which require a prefilled syringe, in general, are intended only for a single administration of a fixed dose. If a prefilled syringe needs to be assembled into an autoinjector, then physical compatibility between the prefilled syringe and autoinjector should also be evaluated.

In addition to their user friendliness, auto injectors offer sterility assurance, a low chance of contamination, increased product yield, and can be a good choice for delivery of highly viscous biological drugs given their even and controlled pressure profile. However, these devices carry a higher price tag when compared to prefilled syringes and vials.

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How to bridge vials with prefilled syringes

Another factor that must be considered when switching to pre-filled syringe are the materials used in their manufacture, as the product format involves migration from another product format, such as a vial. An evaluation should be conducted that ensures the materials in the selected syringe are comparable to those of the vial used in the initial phases of product development. The analysis should specifically consider:

- How the material in the proposed syringe, including the needle, needle shield, or Luer Lock components, can negatively impact the drug product stability
- How any newly introduced materials can interact with drug product
- If any change in the formulation will be needed (as the case of changing from lyo powder to liquid formulation)

Choosing a container and closure system made up of the same materials as the combination of vial and stoppers will limit the need for additional extractable and leachable studies. Any new materials, including those in the needle shield or needle, will need to be evaluated in a leachable study to be performed in accelerated conditions. If the barrel of the syringe is made of polymeric matrix instead of glass, extractable studies also must include proposed labels, adhesive, and ink

In addition to a preliminary screening of the material, the compatibility between the drug and tungsten as well between the drug and silicon oil need to be assessed in accordance with the points previously outlined. Several different combinations of plungers and syringes should be submitted for an accelerated stability study. This will not only determine drug product compatibility but also help make a final decision about the selected primary container. which must meet various requirements apart the chemical compatibility, such as container closure integrity, heat resistance, shock resistance, and plunger gliding forces.

Once the final configuration of prefilled syringes and plungers is selected, then a study assessing compatibility, stability, and other functionality properties of the finished product needs to confirm the suitability of the choices done and the safety of the new presentation.

Conclusion

Moving final product presentation from vials to prefilled syringes can lead to many patient, healthcare provider, and drug manufacturer benefits. However, there are many challenges when managing the transition from a vial to a prefilled syringe.

An accurate analysis of the critical parameters that can affect the overall stability of the final presentation in a prefilled syringe prevents one from wasting valuable resources while also driving the selection of the most appropriate primary packaging for the successful commercialization of a drug product.

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