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Developing a Robust Manufacturing Process for Pre-filled Syringe Biologics

CHALLENGES AND MITIGATIONS

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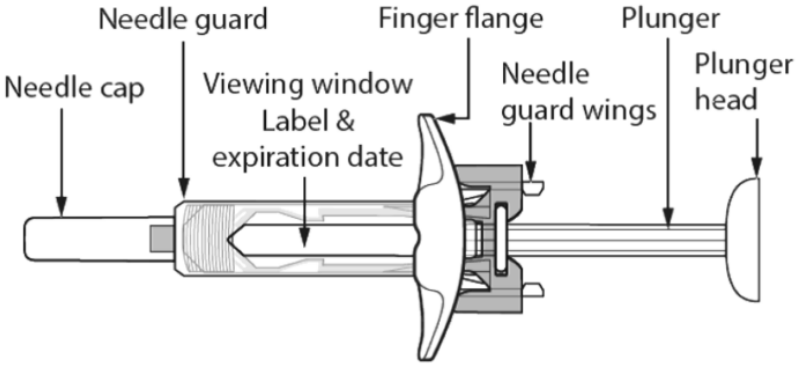
Introduction

A prefilled syringe (PFS) is a disposable syringe that comes preloaded with a specific dose of medication, ready for injection. This design simplifies the process of administering injectable drugs, as it eliminates the need to draw medication from a vial into a syringe before use.

A typical configuration showing the basic components of a PFS is given in Figure 1.

The syringe barrel is either made from Type 1 borosilicate glass or a plastic such as polypropylene, cyclic olefin polymer or cyclic olefin copolymers. Plunger and tip cap are made of (surface coated) elastomeric materials. Syringe barrels and plungers are typically coated with an agent (e.g. silicone oil) to facilitate plunger movement. Plunger movement is accomplished by an attached piston rod (typically plastic).

FIGURE 1 - SCHEMATIC REPRESENTATION OF PFS



A PFS has several practical advantages over vial and syringe combinations in terms of safety, accuracy, convenience, and cost efficiency, making them a preferred choice in many medical settings.

Regulatory Definitions

The US Food and Drug Administration (FDA) defines a container closure system as "the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components" [1]. A similar definition of container closure is given by the EMA: "the sum of packaging components that together contain and protect the active substance or the dosage form. This includes immediate packaging components and secondary packaging components, if the latter are intended to provide additional protection to the active substance or to the drug product" [2].

It is clear from these definitions that a prefilled syringe meets the definition of a container–closure system and thus is subject to the associated guidelines and regulations.

Foremost among these regulations and guidelines are the regulatory expectations that revolve around suitability for the intended use. As noted in FDA's container–closure guidance: Every packaging system should be shown to be suitable for its intended use: it should adequately protect the dosage form; it should be compatible with the dosage form; and it should be composed of materials that are considered safe for use with the dosage form and the route of administration. If the packaging system has a performance feature in addition to containing the product, the assembled container closure system should be shown to function properly.

Market for PFS

Recent advancements in technology have revolutionized the Prefilled Syringe (PFS) market, driving unprecedented growth not only for pharmaceuticals but also for biopharmaceuticals. The global "Pre-Filled Syringe (Prefilled Syringe) Market" achieved a valuation of USD 67 Billion in 2023 and is projected to reach USD 131.99 Billion by 2031, demonstrating a compound annual growth rate (CAGR) of 10.17% from 2024 to 2031 [2]. There is a strong focus on designing PFS that improve patient comfort and adherence. Features like easy-to-use autoinjectors and ergonomic designs are becoming more common. With the shift towards home healthcare, there is a significant trend towards developing PFS that patients can use themselves, reducing the need for healthcare professional intervention.

Benefits of the PFS

BENEFITS FOR USERS

- **Enhanced Safety:** Ease of use, minimizes handling time and reduces the risk of microbial contamination.
- **Contamination Prevention:** Prevents drug solution contamination from debris caused by needle piercing the rubber stopper.
- **Accurate Dosing:** Ensures highly precise dose delivery.

BENEFITS FOR MANUFACTURERS

- **Manufacturing Advantages:** Traditional vial-based formulations often require 10% to 25% more drug per vial to account for losses during administration. Prefilled syringes (PFS) need only 2-5% overfill, significantly reducing drug use and production costs, which is particularly beneficial for biopharmaceutical manufacturers with high production expenses.
- **Easy Transportation:** PFS are lighter and more compact, making them easier to handle, store, and transport, thereby lowering transportation costs.
- **Flexible Product Lifecycle Management:** PFS allow drug manufacturers to differentiate their products and manage production cycles more effectively. Full life cycle management of biologics for biotech or biopharma. Many biotech companies initially launch new products in standard vial packaging and later transition to PFS for second-generation products or to stand out from competitors.

BENEFITS FOR R&D

- **Enhanced Protection:** With smaller headspace, the shear force during the transportation of PFS will be significantly smaller.
- **Reduced Oxidation:** PFS with vacuum stoppering have smaller headspace and less residual air, reducing the gas-liquid interface. This is beneficial for biological products that are easily oxidized and sensitive to shear.
- **Improved Sliding Force:** PFS provide better sliding force, making them suitable for high concentration and high viscosity biologics.
- **Flexible Packaging Options:** PFS offer more flexible packaging choices, including product-specific and customizable injection pens.
- **Convenience leads to better treatment adherence:** Combined with injection pens, it is convenient for patients to use and enhances patient compliance.

When to Select a PFS During Drug Development

DOSAGE FORM SELECTION FOR DIFFERENT CLINICAL STAGES.

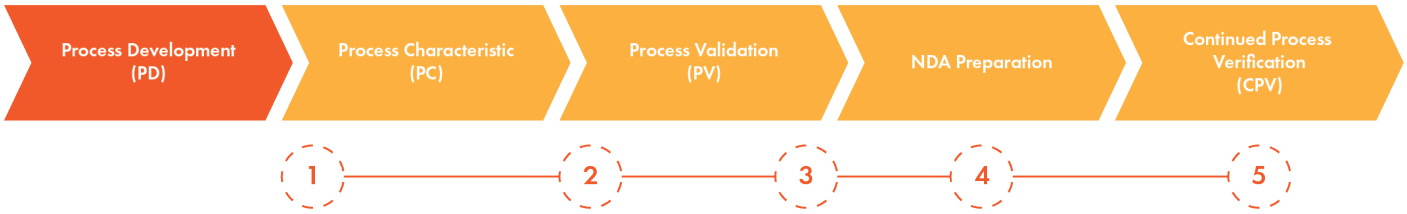
PFS are typically considered during the clinical Phase II of drug development. In the early phases, vials are recommended, with a switch to PFS ideally occurring before pivotal clinical trials. During IND Clinical Phase I, vials are preferred for formulation packaging due to several reasons: dose ramping requires multiple doses, which would necessitate preparing several PFS; using multiple PFS sizes, manufacturing processes, and batches can significantly increase Chemistry, Manufacturing, and Controls (CMC) costs; and releasing and investigating multiple batches of PFS drug products (DP) for stability adds complexity and can hinder rapid clinical progression.

CMC DEVELOPMENT STAGES FOR PFS

The development of PFS within the CMC framework involves several critical stages to ensure the safety, efficacy, and quality of the final product. In the early development stage (preclinical to clinical phase I), the focus is on proof-of-concept and safety. This involves small-scale production of the drug for initial trials, preliminary formulation development, and initial stability studies to ensure the drug's compatibility with the syringe materials. During clinical phase 2, the objective is to expand trials and refine processes.

This includes scaling up production to support larger clinical trials, optimizing the formulation and manufacturing processes, and conducting more extensive stability studies and compatibility testing. In the late-stage development as indicated in Figure 2, the goal is to prepare for regulatory submission and commercialization. This involves full-scale manufacturing, finalizing the formulation, manufacturing process, and container closure system, and performing rigorous testing for extractables and leachables (E&L), sterility, and stability to meet all regulatory requirements.

FIGURE 2 - PFS STUDY AT LATE STAGE OF DEVELOPMENT



1. Characterization of the PFS filling process
2. Formulation prescription robustness study
3. Compatability studies of pharmaceutical
4. Extractable and leachable studies
5. Forced degradation and stability studies
6. Container closure integrity test (CCIT)

1. Aseptic process Simulation (APS)
2. Process performance qualification (PPQ)
3. Process validation of sterilization filtration (filters)
4. Transportation simulation and validation
5. Formulation Packaging Validation

1. Stability Study

1. Continued Process Verification (CPV)

Considerations for PFS Formulation Development

As with all formulations, when developing a PFS formulation it is important to always keep the route of administration and dose in mind; for example, intravitreal, subcutaneous and intravenous injections may require different formulations in terms of concentration, viscosity, pH and osmolality to ensure patient safety and comfort. Other aspects for considerations include the stability of the active substance and the compatibility of the formulation with the syringe and needle.

CONTENT	CHALLENGES	RECOMMENDED STUDIES & RISK MITIGATION STRATEGIES
Concentration and Dose	PFS subcutaneous injection volumes are typically 1-2 mL, requiring the same dose to be administered in a much smaller volume compared to conventional intravenous antibody dosing. Reducing the volume requires an increase in concentration, which can cause some biologics to become highly viscous, potentially affecting product stability and making administration more difficult.	Excipient Selection
Stability of the molecule	Biologics contained in a PFS are often highly concentrated samples injected subcutaneously and require consideration of factors related to the intrinsic properties of the molecule (e.g., solubility), device/ materials components, and manufacturing processes. These factors can limit protein concentration or lead to protein degradation, aggregation, or formation of visible particles.	Agitation, thermal stress evaluation
Packaging materials compatibility	Considering drug molecules are exposed to additional new materials such as silicone oils, tungsten and adhesives, the risk of reduced stability is higher compared to packaging in vials. Ensuring that the materials used in PFS do not interact negatively with the drug component is crucial. This includes assessing the potential for chemical reactions and ensuring biocompatibility. Conducting comprehensive compatibility studies during the development phase can identify potential issues.	Spiking silicone oils/tungsten, compatibility study. Selecting materials with proven compatibility and using coatings or barriers to prevent interactions can mitigate risks.
Clinical application	The viscosity of biological products with high protein concentrations is typically much higher than that of water. The increased viscosity affects injection performance: for a given syringe size, injection force and injection time can only be reduced by increasing the internal diameter of the needle and, to a lesser extent, by decreasing the length of the needle. However, there are limitations to increasing needle size: it can increase pain and lead to a competitive disadvantage of the product.	Syringe function, injection force evaluation. Increasing the needle wall thickness can expand the needle's inner diameter (I.D.) while keeping the outer diameter (O.D.) the same, thus enhancing injection performance.
Extractables and Leachables (E&L)	Materials used in PFS, such as silicone oil for lubrication, can interact with the drug, potentially causing contamination. Ensuring that no harmful substances leach into the drug solution is critical. Rigorous testing for extractables and leachables is essential. Manufacturers can use alternative materials with lower risk profiles and implement thorough cleaning and sterilization processes to minimize contamination risks. The presence of extractables and leachables (E&L) can also compromise drug safety.	E&L study

Challenges in Manufacturing PFS packaged Drug Product

With fewer handling steps and ease of use compared with empty syringes, prefilled devices can help reduce medication errors. They do, however, pose challenges in manufacturing and require extensive testing. One such challenge is visual inspection. Due to the smaller headspace, the movement of the drug within the prefilled syringe (PFS) is minimal, making it much more difficult to detect foreign particles in the PFS compared to vials, which have significantly more headspace.

FILLING ACCURACY

Achieving accurate fill volumes is challenging due to factors such as liquid viscosity and environmental conditions. Inaccurate filling can affect drug efficacy and patient safety. To improve fill accuracy, high-precision filling equipment should be used, along with automated systems for real-time monitoring and adjustments. Additionally, applying statistical process control (SPC) methods can help ensure consistency.

During the filling process, droplets may remain at the tip of the filling needle after a sample has been filled (as shown in Figures 3 and 4 below). If these droplets fall off, they could alter the amount of product filled. This issue requires careful attention during the filling process of high-precision drug products.

FIGURE 3

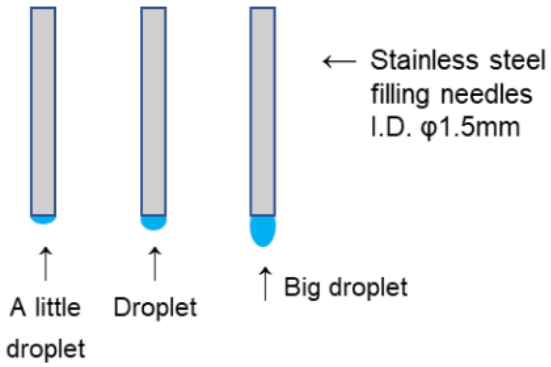
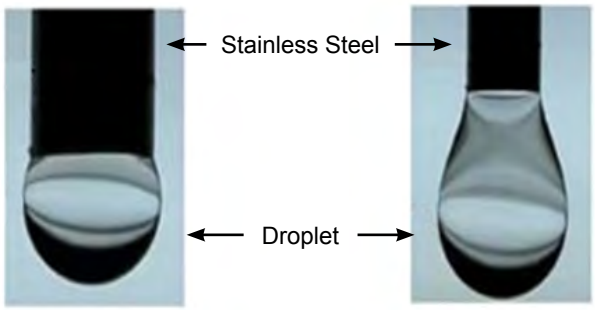


FIGURE 4



INTERRUPTION TIME STUDY

The impact of filling interruption on product quality and production processes must be taken into account while producing high concentration formulations, such as PFS products. A PFS interruption time study evaluates the impact of production interruptions on the quality, stability, and sterility of prefilled syringes. It examines how pauses or delays in the manufacturing process affect fill volume, potential contamination, and product consistency. The study also assesses the stability of the drug, particularly for biologics sensitive to environmental changes, and evaluates sterility assurance to identify any increased risk of microbial contamination. By identifying critical points where interruptions are likely to occur, the study helps optimize the manufacturing process, reduce downtime, and improve efficiency. Additionally, it ensures compliance with regulatory standards, confirming that interruptions do not compromise the product's safety and efficacy. This comprehensive analysis enables manufacturers to implement strategies to mitigate risks and maintain the consistent quality of prefilled syringes.

Highly concentrated protein liquids are prone to losing water at the surface and solidify (see Figure 5 and Figure 6 below). If the filling process is interrupted for an extended period, these concentrated liquids can easily solidify on the inner wall of the filling needle, forming a clog (see Figure 7 below). This leads to non-uniform filling (see Figure 8 below).

FIGURE 5

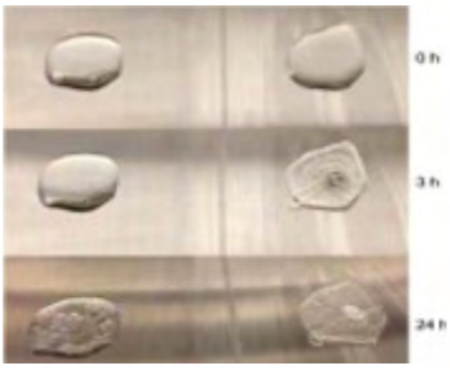


FIGURE 6

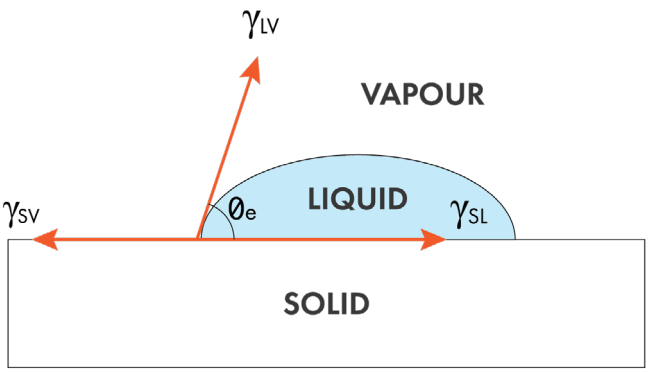
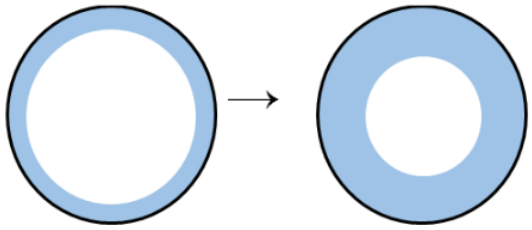
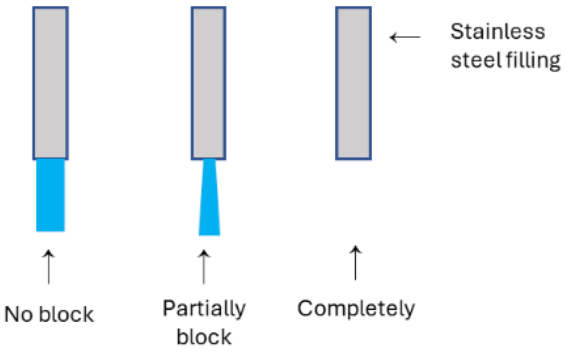


FIGURE 7



Clogging due to accumulation of fluid inside the needle

FIGURE 8



NEEDLE CLOGGING/SYRINGE CLOT

For highly concentrated protein products, one of the risks associated with using PFS with needles is "needle clogging/syringe clot." This issue can prevent the drug solution from being pushed smoothly, thereby failing to meet clinical use requirements. Needle clogging can occur incidentally, such as when the drug solution enters the needle cavity during the filling process. During storage, fluctuations in syringe pressure and increased moisture at the needle tip can lead to protein coagulation (see Figure 9 below) [7]. Additionally, air/liquid segmentation can also cause needle clogging.

Optimizing the filling process by selecting the appropriate headspace can effectively reduce risks.

Additionally, using conical needles can help prevent clogging.

Neutron imaging techniques can be employed to examine the location of needle clogs. These techniques work by taking advantage of the fact that thermal neutrons are strongly attenuated by elements like hydrogen and carbon, making them difficult to penetrate. In contrast, materials with high atomic mass, such as iron and lead, allow neutrons to pass through more easily. As a result, neutron radiography is used to inspect areas shielded by heavy metals, enabling the clear detection of hydrogen atoms within the molecular structure. As illustrated in Figure 10 below, the needle is not completely filled with fluid, and a small amount of fluid has solidified in the needle, resulting in a clog.

FIGURE 9

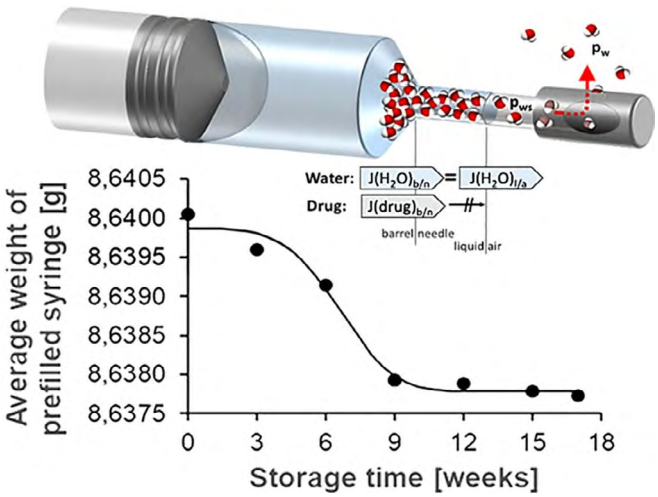
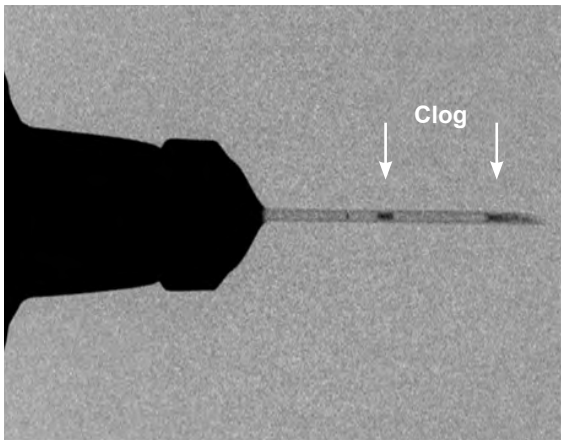


FIGURE 10



Regulatory Landscape & Compliance

The regulatory landscape for PFS differs between the USA, EU and China. In the USA, the FDA regulates PFS as combination products, treating them as both a drug and a device. The primary mode of action (PMOA) determines whether the Center for Drug Evaluation and Research (CDER) or the Center for Devices and Radiological Health (CDRH) takes the lead. The FDA mandates rigorous testing for safety, efficacy, and quality, including extractables and leachables (E&L) testing, sterility assurance, and stability studies.

In the European Union, the European Medicines Agency (EMA) and national competent authorities oversee PFS regulation. Under the Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR), PFS are classified based on their intended use and risk, necessitating compliance with both medicinal product and medical device regulations.
The EMA emphasizes conformity assessments conducted by notified bodies to ensure that safety and performance standards are met, with specific guidelines for drug-device combination products.

In China, the National Medical Products Administration (NMPA) is responsible for regulating PFS, aligning more closely with international standards while maintaining unique local requirements.

Furthermore, the applicant needs to focus on the Exposure Control Plan (U.S. Needlestick Safety and Prevention Act (2000), which mandates the identification, evaluation, and use of safer medical devices to help reduce or eliminate the incidence of needlestick injuries).

Conclusion

Developing a robust manufacturing process for pre-filled syringe biologics is a complex and multifaceted challenge that involves ensuring product stability, achieving precise fill volumes, and addressing the intricacies of visual inspection and foreign particle detection. The added pressure of meeting stringent regulatory requirements for safety, quality, and efficacy further complicates the process.

Navigating the regulatory landscape across regions such as the US, EU, and China requires careful attention to both drug and device regulations. Staying updated with evolving guidelines and collaborating with regulatory bodies is key to maintaining compliance. Additionally, implementing a strong quality management system (QMS) and conducting regular audits help ensure that high manufacturing standards are consistently met. By focusing on continuous process optimization, quality assurance, and adherence to regulatory standards, these challenges can be effectively managed in ensuring the safe and reliable delivery of biologic therapies to patients.

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About Scendea.

Scendea is an international product development and regulatory consulting group serving the pharmaceutical and biotechnology industry.

We are committed problem solvers, redefining the meaning of customer service, with a focus on reducing time-to-market and minimising development costs. Our scientific excellence, industry experience, and collaborative approach enable us to deliver high-quality innovative solutions aligned with jurisdiction-specific regulatory requirements.

Scendea's international team offers strategic and operational support in the fields of Non-clinical, CMC, Clinical, and Regulatory to successfully guide products from early development to marketing approval.

At Scendea, we collaborate, innovate, and together with our clients, we succeed.

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With over 400 skilled employees, Chime Biologics leverages its comprehensive capabilities and internationally-recognized expertise to provide one-stop integrated solutions to worldwide customers. Relying on cell line development and advanced technology development from its Shanghai Innovation Center and proven success in IND-enabling through BLA filing at its Wuhan campus, Chime Biologics is providing high-quality pre-clinical, clinical and commercial manufacturing solutions.

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