Physical and Physiochemical Interactions Between Pre-Filled Syringe Components and Drug Products

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Introduction:
The physical and physicochemical interactions occurring between the components of pre-filled syringes and drug products can have a large impact on device design, patient safety and comfort. Understanding these interactions is crucial for ensuring any drug formulations delivered via pre-filled syringes doesn't have an adverse effect on the syringe performance. The pre-filled syringe act as both a drug delivery device as well as the primary packaging container. Various factors such as material compatibility, extractable and leachables, and device design can influence these interactions. The breakdown below highlights the importance of characterising and optimising pre-filled syringe components to mitigate potential adverse effects on drug product quality and patient health.

General Considerations / Interactions:
Some drug-device interactions are not limited to specific components, these potential interactions can include viscosity, pH, concentration, and ionic strength of the drug solution, which can affect how it behaves in contact with materials like glass, plastic, rubber, and steel. The size of the contact surface area between the drug and syringe components also plays a role, as there are larger contact areas (syringe barrel) and smaller contact areas (needle). The composition of the syringe contents can impact how it interacts with the components. Some examples include active pharmaceutical ingredient (API), water, buffer, surfactant or antioxidant. Considerations should be made to how the drug and devices interact (including sterility) over time and during transportation. For finished products, a biological hazard assessment is recommended (ISO 10993-1) as well as determination of the deliverable volume, ensuring that the device doses accurately and via the correct pathway. Particulates should be also considered, both visible and subvisible, against the relevant pharmacopeia's (USP788 for example).

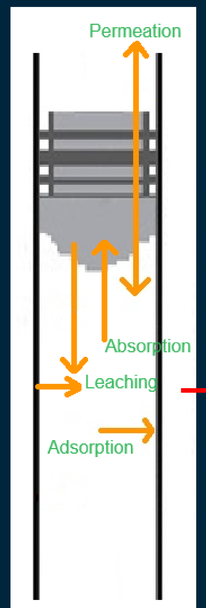
Material Compatibility:
Evaluating material compatibility for pre-filled syringe components is needed to ensure the safety, effectiveness, and stability of the drug product. This involves evaluating how the component materials interact with the drug formulation, as well as understanding potential risks such as degradation, leaching, and impact on drug potency. Key components of a syringe include the barrel, plunger stopper, needle, lubricants and needle shield / tip cap.

Auto-Injector Compatibility:
If the syringe is intended to be used with an auto-injector device, extra considerations need to be made to ensure the device functions as intended. Limitations of using an auto-injector include syringe size (less than 3ml), drug product viscosity (less than 10cp) and the area / depth of injection (subcutaneous). The injection time of a dose can be impacted by the spring strength, drug viscosity and needle dimensions.

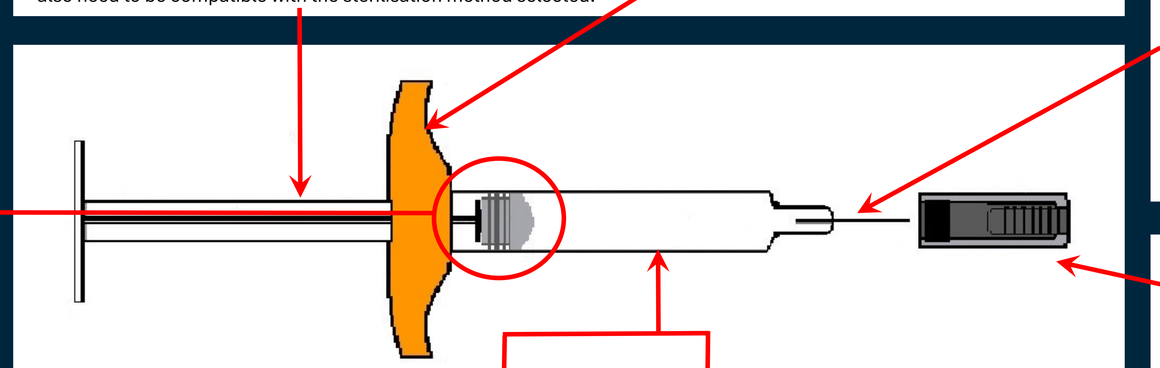
Permeation:
The permeation properties of a plunger stopper needs to be considered when selecting the type of plunger stopper being used. Plunger stoppers act as a barrier to contaminants such as air and moisture, they are essential in maintaining the integrity of the drug product. Butyl plunger stoppers are commonly used for their low permeability properties.

Absorption:
Absorption of the drug product into the elastomeric stopper can cause issues with the drugs potency and stability. Large molecular products (like proteins) are less likely to be affected by absorption but some stabilising excipients can be susceptible to this.

Adsorption:
Adsorption is the process in which drug molecules adhere to surfaces, in this case the plunger stopper and syringe barrel. Issues caused by adsorption include reduction in concentration of active pharmaceutical ingredient and denaturation or aggregation of proteins due to molecular structural changes.



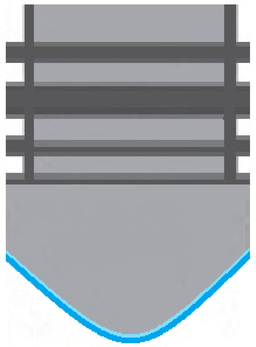
Plunger Rod, Backstop, Flange and Finger Grip:
While the plunger rod, backstop, flange and finger grip don't directly interact with the drug, the design and geometry has an impact on the physical performance of the pre-filled syringe as well as user experience and integrity of the device. For example, with Break Loose and Glide Forces uneven movement of the plunger rod can cause additional forces. These components will also need to be compatible with the sterilisation method selected.



Needle:
There are many aspects of needles that can affect the functionality of a pre-filled syringe. Needles can be either staked or hypodermic needles can be attached via a Luer connection separately. The needle gauge, wall thickness, inside diameter, siliconization, bevel design and any potential defects can all impact the delivery of a drug to the end user.
Patient comfort is affected by the needle bevel design and any defects that are present, this can include burrs and hooks on the needle point. Needle gauge, wall thickness and inside diameter will need to be considered when using high or low viscosity drugs. The combination of a high viscosity drug and small needle gauge can cause issues with high break loose and gliding forces.

Needle Shield or Tip Cap:
The needle shield or tip cap, depending on if a staked needle is present, will need to have its dimensions, geometry and materials carefully considered. These can have a significant impact on the cap removal force and the sterilisation compatibility.

Plunger Stopper Films and Coating:
Films and coatings are applied to plunger stoppers as a barrier minimising the interaction between the plunger stopper and drug product and maintaining container closure integrity. A film is laminated to the plunger stopper during moulding, whereas the coating is a liquid or vapour that is either sprayed, tumbled or vapour deposited on to the component. Generally, these barriers are fluoropolymers and provide a barrier from extractables and leachables as well as minimising the interaction between plunger stopper and drug product. This can extend the shelf-life of the drug and maintain its potency, both of which are affected by absorption and adsorption.



Extractables & Leachables:
Extractables and Leachables are critical considerations in pre-filled syringe component selection, as they can impact the safety and efficacy of pharmaceutical products. Extractables are organic or inorganic compounds that can be extracted from syringe components and materials under forced or worst-case conditions. Leachables, on the other hand, are compounds that migrate from the components or materials into the drug product under normal conditions. Both can pose risks; extractables may contribute to elemental impurities and interact with the active pharmaceutical ingredient (API) or excipients, while leachables can interfere with proteins, leading to aggregation or denaturation, react with the API causing a loss of efficacy, and even inhibit cell growth. Additionally, leachables can interfere with drug assays, increase impurity levels, alter pH, cause precipitates, and interfere with medical diagnostic tests. Although no container is entirely free of extractables and leachables, these factors must be evaluated on a case-by-case basis to minimize risks and ensure product safety.

Syringe Barrel:
The syringe barrel, which can be made from either glass or plastic, is the largest area of drug contact on the device. Considerations should be made to whether the drug is light-sensitive and if the sensitivity can significantly impact aspects of the drug. If so, a coloured barrel (often amber or black) may be required.
Air bubbles, which are generated during the filling process, are frequently seen in pre-filled syringes. Having an air bubble inside the syringe barrel with the drug means that there is oxygen present to potentially interact with it. In general, smaller air bubbles are seen in vacuum stoppering and larger air bubbles are seen in vent tube stoppering. Having an air bubble present in the syringe barrel during transportation may cause the expansion of the bubble, which in turn causes the plunger stopper to move, potentially affecting the container closure integrity of the pre-filled syringe. If the plunger stopper moves enough, it may enter the non-sterile zone (an exposed internal section of syringe barrel), causing the syringe contents to no longer be sterile. For this reason, it is recommended that an air transportation test is conducted (ASTM D6653).

Conclusion
The drug and syringe components can interact in many different ways. This can result in adverse effects on syringe performance and the quality / stability of the drug. All container materials will need to be assessed during the material selection stage to ensure compatibility and no adverse effects. The Fill and Finish process will need to be carefully reviewed to ensure this process has no impact on the functionality of the device or delivery of the drug to the patient. It is recommended that Stability (ICH Guidelines) and Transport studies (ASTM D4169) are carried out.

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