Plastic Pre-filled Syringes: *Clinical Advantages, Technical Requirements, and Material Selection Criteria*

In the last decade, the use of plastic pre-filled syringes for parenteral administration has been steadily growing. In fact, the compound annual growth rate (CAGR) specific to the plastic segment is estimated to be between 11.5% and 13.8%.

This is understandable when considering and analysing the numerous advantages offered by pre-fillable syringes.

Firstly, contamination risks are reduced because fewer steps are required for medication preparation. This allows for direct drug administration to the patient, avoiding the stages of solution reconstitution and inoculation, and proceeding instead directly with administration. Secondly, pre-fillable syringes allow the operator to inject a dose of medication with high precision, as it is possible to fill the syringe with the exact amount needed for the treatment. This provides advantages in terms of both administration and dosage, avoiding drug waste and facilitating delivery operations.

Glass vs. Plastic Syringes

For decades, glass was the material of choice for pre-fillable syringes due to its high transparency, high chemical resistance, low alkali content, and barrier properties suitable for the long-term storage of vaccines and other pharmaceutical products. On the other hand, glass exhibits high sensitivity to cracking and breakage, as well as the risk of delamination, which constitutes a source of chemical and physical contamination for the drug or substance it contacts.

Furthermore, glass syringes present high levels of tungsten residue near the needle at the Luer Cone connection, which can lead to aggregation phenomena in the case of protein-based drugs. To address these issues, plastic solutions have entered the syringe market – and specifically the pre-filled syringe market – over the last decade.

The most commonly used polymers are:

- Polypropylene (PP)
- Polycarbonates (PC)
- COC (Cyclo-olefin copolymer)
- COP (Cyclo-olefin polymer)

The choice of which plastic to use for a product is directly related to its intended purpose and final use, as well as the intrinsic characteristics of the material. To select the suitable plastic type, one must first consider the final use and the type of solution it will contact.

For a proper evaluation, it is first necessary to identify the "intended use" of the solution or drug the pre-filled syringe will contain. In this initial phase, the syringe is considered primary packaging, and it is then considered a medical device once pre-filled with the solution or drug. To establish the suitability of the plastic, it is necessary to understand how the solution enters into contact with blood or tissues and the duration of exposure.

Based on these characteristics, the plastic must be evaluated for:

- Particulate release
- Biocompatibility

This is to understand the type of interactions that may be triggered, which could lead to drug degradation, protein precipitation (especially for protein-based drugs), decreased shelf-life, and a reduction in the activity of the active ingredient or other components of the solution. For this assessment, various chemical, physical, and biocompatibility tests must be performed to identify the material and particle content in the primary packaging and ensure biological compatibility for end-user safety.

Foreign Particulate Matter Testing

Tests aimed at identifying particulates follow Pharmacopoeia directives. According to regulations, particles of the following sizes are evaluated:

- ≥ 10 µm;
- ≥ 25 µm;
- ≥ 50 µm

The ranges vary based on the drug's intended use. Specifically, the reference standards for identifying particulate content are:

- USP <788> – Particulate Matter in Injections: Evaluates the presence of mobile, undissolved substances (other than gas bubbles) that may derive from various sources like contamination. In this case, particulate levels must be minimised and controlled regardless of type.

- USP <790> – Visible Particulate Matter in Injections: Concerns visible particulate matter. Its primary purpose is to define what is meant by an injectable pharmaceutical product being "essentially free" of visible particles. This is a critical safety standard, as foreign particles (such as glass, metal, or fibres) can cause serious medical complications, including embolisms or inflammatory reactions.

- USP <789> – Particulate Matter in Ophthalmic Solutions: Unlike USP <790>, this focuses on sub-visible particulate matter – particles too small to be detected by the human eye but potentially dangerous for ophthalmic solutions. These solutions have stricter directives due to the potential for endophthalmitis and corneal lesions.

It is therefore necessary to entrust the analysis of the primary packaging (syringe) to specialised laboratories to evaluate whether the particulate matter present complies with regulations. To increase performance, particularly for ophthalmic solution production, it is advisable to mould plastic components in ISO 7 classified cleanrooms to further limit particulate contamination.

Extractables and Leachables Testing

A second aspect to evaluate, based on the material's intrinsic properties in contact with the solution, are:

- **Extractables:** Chemical compounds that can be released from a contact material under aggressive or exaggerated laboratory conditions.
- **Leachables:** Compounds that can migrate into the drug during normal use.

- Reference can be made to the ISO 10993-18 standard or, specifically for

plastic materials, to USP <661.2>: Plastic Packaging Systems for Pharmaceutical Use. As with particulates, the release of these materials could compromise the stability of the solution, potentially modifying the pH, the activity of the active principle, or other components, thereby reducing the drug's efficacy and shelf life.

Biocompatibility Testing
The chosen plastic must be biocompatible. Reference is made to the ISO 10993 standard, which describes the biological evaluation of medical devices within a risk management process. This includes assessing aspects such as haemolysis, cytotoxicity, skin irritation, and toxicity.

In light of the cases described, it is important to choose the appropriate type of plastic for the specific solution and intended use:

Polypropylene (PP)
Polypropylene is widely used for its chemical and physical properties, as it resists erosion from various materials. Its performance remains optimal even in high-temperature and high-humidity contexts, which helps ensure instrument safety. It is compatible with several sterilisation methods, such as:

- Autoclave (cycles at 121°C)
- Gamma radiation
- EtO (Ethylene Oxide)

The choice of PP for syringes is also supported by its biocompatibility and cytotoxicity characteristics. PP syringes commonly contain generic drugs such as saline solution (e.g., pre-fillable syringes for flushing operations), heparin, atropine, and epinephrine in small volumes, and electrolytes like sodium bicarbonate in larger volumes for hospital and emergency use.

Cyclic Olefins (COC and COP)
While polypropylene remains the material of choice for low-cost drugs, diluents, and electrolytes, cyclic olefins have become the preferred plastic for new drugs. These are divided into Cyclic Olefin Copolymers (COC) and Cyclic Olefin Polymers (COP).

COC are transparent amorphous copolymers based on cyclic and linear olefins. They exhibit a unique combination of properties, including high transparency, low density, excellent moisture barrier capabilities, and resistance to aqueous and polar organic media.

COP, is distinguished by:

- **High transparency:** Light transmission comparable to glass, essential for visualising the solution inside the primary packaging. This makes it preferable to polypropylene, which has lower light transmittance.
- **High break resistance:** Compared to glass, the breaking point is higher, and the failure mode is different (glass shatters into multiple pieces), making it safer for users.
- **Greater resistance to low temperatures:** Compared to PP, it resists temperatures as low as -194°C, allowing for low-temperature storage.
- **Low impurity levels.**
- **Low residual metal levels:** Lower than PP and other plastics, and lower tungsten levels than glass, improving performance with protein-based drugs.
- **Absence of delamination:** Avoiding the critical phenomenon of microscopic flakes detaching from the internal surface.
- **Sterilisation compatibility:** Compatible with Gamma radiation, steam, EtO, and E-beam.
- **High moisture barrier.**
- **Low levels of protein absorption and aggregation:** Preventing the compromise of drug efficacy and stability.

In conclusion, plastic syringes are significantly increasing due to characteristics that allow for wide use in the pre-filled syringe field, providing notable advantages in clinical and home settings. Therefore, the choice of the appropriate plastic type is decisive in meeting needs related to both cost and performance regarding drug interactions, as well as the ability to keep characteristics unchanged from the filling process to final use.

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