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PREFILLED SYRINGES: ADVANCEMENTS IN DRUG – DEVICE COMBINATION SYSTEMS

Shubhangi. S. Hambharde[1], Khan Hajera *, Metku shriveni[1], Sarthak Gawande[1], Joshi Sheetal[1], Kubde Kanchan[1], Manoj Honsangde[2], Lolge Shruti[2], Kakde Vikas[2], Gharke Karan[2].

Department of Pharmaceutical Quality Assurance SSS Indira College of Pharmacy, Nanded-431601, Maharashtra, India.

Affiliated to Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra, India.

Abstract:

Prefilled syringes (PFS) have undergone a paradigm shift, transitioning from passive primary container closure systems into complex, integrated drug-device combination products designed for modern biopharmaceuticals. Their ready-to-administer presentation streamlines clinical workflows, ensures rigorous dosing precision, minimizes contamination risks, and facilitates patient-centric home self-administration. The rapid proliferation of therapeutic monoclonal antibodies, recombinant proteins, peptides, and high concentration subcutaneous formulations has underscored the vital importance of container contact materials, silicone lubrication dynamics, needle geometry, and mechanical device integration. Contemporary PFS platforms encompass traditional Type I borosilicate glass, cyclic olefin polymer (COP), cyclic olefin copolymer (COC), and specialized silicone-reduced or silicone-free platforms. Each material matrix presents a distinct trade-off regarding gas/moisture barrier properties, fracture resistance, dimensional tolerances, extractables (E&L) profiles, and interface-induced drug degradation. For biological macromolecules, drug-container compatibility represents a critical quality attribute (CQA); protein adsorption and interfacial denaturation at glass, polymer, elastomer, air-liquid, and silicone-oil interfaces frequently induce subvisible particle generation and irreversible aggregation. Silicone oil microdroplets remain a focal technical challenge due to potential migration and nucleation effects, while residual manufacturing contaminants such as tungsten species can induce localized protein unfolding. Concurrently, injectability functionality is paramount for viscous high-concentration biologics, were hydraulic resistance and extrusion dynamics scale critically with needle lumen diameter and fluid rheology. This review provides a comprehensive review covering component architecture, material interaction pathways, silicone dynamics, fluid mechanical modelling, clinical human factors, regulatory frameworks, and next-generation smart delivery devices

Keywords: *Prefilled syringe; Drug-device combination system; Primary container closure; Biologics stability; Monoclonal antibodies; Silicone oil migration; Cyclic olefin polymer (COP); Injectability mechanics; Autoinjectors; Extractables and Leachables (E&L)*

Corresponding author:

Hajera Khan,

Department Of Pharmaceutical Quality Assurance, SSS Indira College of Pharmacy, Nanded – 431601, Maharashtra, India.

Mobile:

Email Id: *khan.hajera@rediff.com*

QR CODE

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INTRODUCTION:

Parenteral drug administration is experiencing a substantial evolution towards patient-centric, ready-to-use delivery systems that improve dosing precision, sterility assurance, and ease of self-administration. The conventional vial-and-syringe workflow entails multiple handling steps, increasing risks of contamination, dosing inaccuracies, and operational complexity. Prefilled syringes (PFS) have transitioned from mere primary containers to intricate drug–device combination products by integrating the pharmaceutical formulation directly within the administration device during primary packaging [1,2]. This shift streamlines clinical practice, minimizes aseptic breach risks, and supports home-based self-injection.

The growing use of complex biologics, such as monoclonal antibodies, recombinant proteins, and high-concentration subcutaneous formulations, markedly elevates the technical demands on PFS design and material selection. These biological macromolecules are sensitive to interfacial stressors—including interactions at glass, polymer, air-liquid, and silicone oil interfaces—as well as exposure to trace contaminants like tungsten, which may provoke protein aggregation, structural unfolding, and immunogenic responses [3]. Moreover, high viscosity formulations challenge the syringe injectability profile, necessitating optimization of needle geometry and lubricant systems to ensure feasible manual or automated delivery forces [5].

The contemporary PFS therefore mandates a holistic view as an integrated system, where each subcomponent—barrel material, elastomeric plunger, lubricant, needle, and tip cap—directly influences product stability, safety, and mechanical function over shelf life [6]. While Type I borosilicate glass remains the benchmark due to its gas impermeability, dimensional stability, and optical clarity, it entails drawbacks such as brittleness, glass delamination, silicone oil dependency, and potential tungsten contamination originating from manufacturing processes [7]. Alternatively, cyclic olefin polymers (COP/COC) offer superior break resistance, low protein binding, and opportunities to minimize or eliminate silicone oil usage; however, their higher permeability to oxygen and moisture necessitates advanced secondary packaging approaches [8].

This review article synthesizes recent advances in PFS component engineering, drug–device compatibility, injectability science, and integration with autoinjector and wearable platforms, charting a roadmap for next-generation systems that ensure reliable, safe, and patient-acceptable biologic drug delivery [9].

Prefilled syringes (PFS) have undergone a significant evolution from being passive primary containers to complex integrated drug-device combination products designed for modern biopharmaceutical therapies. The ready-to-administer nature of PFS improves clinical workflows by minimizing dosing errors, reducing contamination risks, and supporting patient-centric self-administration, especially in home-care environments. This transition is driven by the growing use of monoclonal antibodies, recombinant proteins, peptides, and high-concentration subcutaneous formulations, which impose stringent requirements on container materials and device performance [10,11].

Table No 01: - Overview of Current Research Gaps and Future Needs in Drug–Device Combination Systems

Area	Research Gaps and Needs	References
1. **Materials Science**	Comparative long-term stability and robustness studies of glass vs COP/COC vs hybrid systems are lacking.	[12].
2. **Lubrication Alternatives**	Development of effective low-friction systems that minimize silicone oil interaction with proteins for reduced aggregation.	[13].
3. **Predictive Compatibility**	Predictive in vitro screening methods to foresee protein instability due to material attributes are underdeveloped.	[14].
4. **Tungsten Contamination**	Quantification of clinically relevant tungsten exposure thresholds and risk mitigation strategies remain incomplete.	[15].
5. **Injectability Modeling**	Incorporation of realistic patient variability and usability parameters in injection force modeling needs advancement.	[16].

6. **High Concentration Biologics**	Formulation strategies and device technologies to enable feasible subcutaneous delivery of very high concentration and volume doses require further development.	[17].
7. **Advanced Delivery Devices**	Validation of digital feedback systems and smart connected devices integrated with PFS for improved adherence is nascent.	[18].
8. **Sustainability**	Environmentally sustainable, disposable PFS devices with reduced lifecycle impact are needed.	[19].

2.PFS DESIGN MATERIAL COMPONENT:

A prefilled syringe comprises an ensemble of precision engineered sub-components working in concert to maintain sterility, barrier integrity, and mechanical function across the product shelf-life. Galcanezumab, a subcutaneous monoclonal antibody for migraine prevention, has been evaluated using single-dose prefilled syringes (PFSs) and disposable autoinjectors, highlighting the importance of patient-friendly devices for convenient self-administration. PFSs provide ready-to-use, premeasured doses with fewer preparation steps but require manual needle insertion and plunger operation. Autoinjectors offer ergonomic design, locking mechanisms, needle protection, and audible/visual feedback to simplify and standardize injection. Both devices require proper patient training. Overall, the study demonstrates the shift toward patient-centric drug–device systems combining dose convenience, safety, ergonomics, and usability for long-term self-administration. [20].

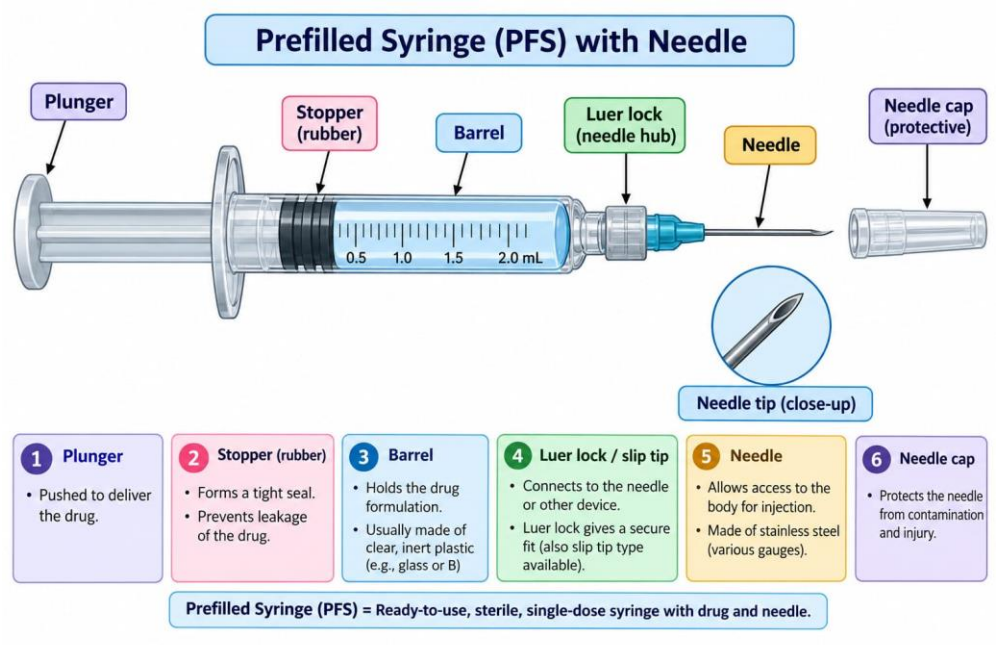


Figure 1: Cross-Sectional Component Architecture of a Prefilled Syringe.
Schematic depicting major mechanical sub-components and product contact interfaces.

2.1 GLASS BARREL CONSTRUCTS TYPE I: -

borosilicate glass remains the historical benchmark due to its high optical clarity, dimensional stability, thermal endurance, and gas impermeability. However, glass presents inherent vulnerabilities: brittleness glass delamination (lamellae formation), weight constraints, and requirement of silicone oil lubrication. Furthermore, glass forming using tungsten pins introduces trace heavy metal risks [21].

2.2 POLYMER BARRELS: COP AND COC: -

Cyclic Olefin Polymers (COP) and Cyclic Olefin Copolymers (COC) represent advanced thermoplastic alternatives. They offer break resistance, high precise molding tolerances, low protein binding, and the ability to eliminate silicone

oil lubrication entirely. However, their oxygen and moisture vapor transmission rates are higher than glass, requiring robust secondary packaging for oxygen-sensitive active pharmaceutical ingredients (APIs) [22].

2.3 ELASTOMERIC PLUNGER STOPPERS AND TIP CAPS: -

Elastomeric stoppers (typically halobutyl rubbers) provide the movable dynamic seal. Fluropolymer film coatings (e.g., Fluorotec) are frequently applied to stopper contact faces to minimize extractables leachability and reduce sliding friction without heavy siliconization [23].

Table No 02: -Characteristics of Primary Materials and Functional Components in Prefilled Syringe Systems

Material/component	Advantages	Limitations / concerns	Typical relevance
1. Type I glass barrel	Established pharmaceutical history; good transparency; strong barrier properties; dimensional consistency	Breakage risk; surface-related particles; usually requires lubrication for low-friction plunger movement	Widely used for small molecules and biologics
2. COP/COC polymer barrel	Low breakage risk; light weight; useful dimensional/functional properties; silicone-free options possible	Higher gas permeability than glass; material-specific E&L; and stability assessment required	Biologics and applications needing robust polymer systems
3. Elastomeric stopper	Provides seal; enables controlled plunger movement	Potential extractables/leachable; adsorption or interaction with formulation; material variability	All PFS configurations
4. Silicone lubricant	Reduces friction and supports smooth injection	Can migrate into formulation; may contribute to protein aggregation/particles in susceptible biologics	Commonly used in glass PFS
5. Cross-linked silicone	Maintains lubrication while potentially improving lubricant retention and reducing particles under stress	Performance can vary by system/vendor; still requires product-specific compatibility assessment	Sensitive biologic formulations
6. Silicone-oil-free glass	Reduces direct silicone exposure; promising for protein stability	May have higher break-loose/extrusion force; specialized stopper/coating may be required	Biologics with silicone sensitivity
7. Needle assembly	Enables direct administration; geometry can be optimized for delivery force and time	Gauge, length and inner diameter affect injection force and delivery time; sharps safety considerations	Manual PFS and autoinjector systems
8. Tip cap / needle shield	Protects needle and maintains system integrity	Material can interact with drug; potential impact on oxidation or E&L; depending on formulation	Staked-needle and ready-to-use PFS
9. Low-dead-volume design	Improves dose utilization and can reduce residual drug	Geometry must maintain reliable sealing and delivery performance	High-value/low-volume biologics

3. DRUG–DEVICE COMPATIBILITY & STABILITY:

Biological drug stability within PFS is governed by complex interfacial thermodynamics. Biologics undergo structural alterations when exposed to hydrophobic surfaces, chemical leachables, and dynamic physical stresses. Prefilled syringes (PFSs) provide accurate, convenient, ready-to-use drug delivery with reduced contamination and drug overfill. For biologics, syringe–drug compatibility is

crucial because silicone and other materials may affect protein stability and cause aggregation or particles. The study showed that cross-linked silicone coating improved syringe integrity and reduced subvisible particles while maintaining monoclonal antibody stability. However, dose accuracy, glide force, dead volume, injection time, and high-viscosity formulations were not experimentally studied and require separate references. Overall, the article supports the importance of PFS design, silicone technology, and drug–device compatibility for biologic stability. [24]

3.1 PHYSICAL STABILITY & SUBVISIBLE PARTICULATES: -

Agitation during transportation induces continuous surface renewal at the air-water and silicone oil-water interfaces. Adsorbed monomeric proteins undergo structural unfolding, exposing internal hydrophobic patches that drive self-association into subvisible (2–100 µm) and visible (>100 µm) particulates [25].

3.2 EXTRACTABLES AND LEACHABLE (E&L) RISK PROFILING: -

Leachable are chemical entities that migrate from container materials into the formulation over shelf-life. Primary sources include rubber vulcanization agents, zinc catalysts, antioxidants (e.g., Irganox derivatives), polycyclic aromatic hydrocarbons, and monomeric residues. Evaluation follows ISO 10993-18 and USP recommendations [26].

Table No 03: - Overview of Key Drug–Device Compatibility Issues, Potential Effects, and Recent Research Findings in Prefilled Syringes

Compatibility issue	Potential effect	Recent research finding / implication	Refs
1. Silicone oil migration	Protein adsorption/aggregation; visible or subvisible particles; possible change in functionality	Cross-linked silicone coatings can improve lubricant integrity and reduce particle generation under agitation; silicone-free systems are also being investigated	[27].
2. Protein–interface interactions	Loss of soluble protein, conformational change, aggregation	Agitation and exposure to silicone-water or air-water interfaces can increase particle formation in susceptible protein formulations	[28].
3. Extractables/leachable	Chemical degradation, toxicity risk or changes in protein quality	A holistic, risk-based E&L; program should combine material knowledge, extraction studies and actual drug-product compatibility testing	[29].
4. Polymer gas permeability	Potential oxygen/moisture sensitivity during storage	Silicone-oil-free polymer syringes provide advantages but gas permeability can be a limitation for oxygen-sensitive biologics	[30].
5. Elastomer interaction	Oxidation, adsorption, leachable-related changes	Closure-material screening can identify product-specific differences; one elastomer may perform better than another for a given biologic	[31].
6. Sterilization effects	Chemical modification or degradation of sensitive proteins	Research has shown that sterilization method can affect protein stability; sterilization strategy should therefore be product-specific	[32].
7. Particulate formation	Quality, safety and potential immunogenicity concerns	2022 research highlights limitations of conventional light-obscuration testing because it may not distinguish silicone particles from proteinaceous particles; flow-imaging-based strategies are being investigated	[33].

8. Excipient–material interaction	Changes in extrusion force and delivery behavior	**material interaction: Comparative functional evaluations demonstrate that cyclic olefin polymer (COP) prefilled syringes maintain more consistent dynamic extrusion forces across diverse buffer and excipient conditions compared to siliconized glass syringes, which exhibit variable glide force profiles due to silicone layer displacement**	[34].
9. High-concentration biologics	High viscosity increases injection force and delivery time	Current research emphasizes an integrated formulation–device approach to maintain both protein stability and deliverability at high concentration	[35].

4. PFS PERFORMANCE & BIOLOGIC FORMULATIONS:

4.1 INJECTION FORCE, GLIDE FORCE AND DOSE ACCURACY: -

PFS performance is determined by the interaction between formulation rheology and mechanical characteristics of the syringe. Key performance parameters include break-loose force, glide force, injection force, injection time and Page 2 dose accuracy. Barrel dimensions, stopper geometry and contact length, lubricant characteristics, needle inner diameter and formulation viscosity can all influence the force required for injection. Dose accuracy is also influenced by dead volume and the precision of filling and delivery components [36].

4.2 DEAD VOLUME AND DELIVERED DOSE: -

Dead volume is the residual volume that remains in the delivery pathway and cannot be practically administered. Minimizing dead volume can improve dose utilization, especially for expensive biologics, but changes to geometry must not compromise mechanical function or CCI. Device qualification should therefore assess delivered dose across representative units and conditions, including the intended operating method and relevant temperature range.

4.3 BIOLOGICS AND HIGH: - concentration formulations: Biologics increasingly require subcutaneous administration at higher concentrations to reduce injection volume and facilitate self-administration. However, concentrations above approximately 100 mg/mL can produce increased viscosity, protein–protein interactions, aggregation risk and greater injection resistance. These properties can challenge conventional PFS and autoinjector platforms. Current development strategies include formulation-based viscosity reduction, protein engineering, alternative excipients, larger-volume subcutaneous approaches and device designs capable of handling more viscous products [37].

4.4 INJECTION TIME AND HUMAN FACTORS: -

Injection time is not merely a mechanical parameter; it can affect usability and patient acceptability. A viscous formulation may require greater force or a longer injection duration. Human-factors **development** should therefore consider hand strength, dexterity, visual feedback, grip, needle concealment, activation sequence and confirmation of dose completion. Recent experimental work indicates that critical component attributes can be optimized to improve injectability of viscous formulations [38].

4.5. INJECTABILITY SCIENCE: -

Injectability defines the force required to extrude a viscous drug formulation through a fine-gauge needle at a target volumetric flow rate.

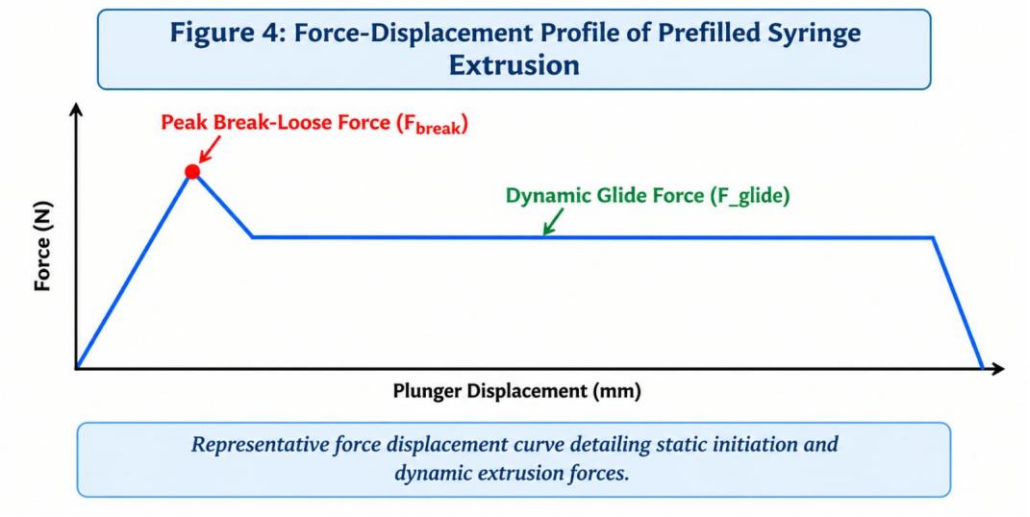


Fig no.2 force-displacement profile of prefilled syringe extrusion

The total extrusion force (F_{total}) is mathematically modeled by combining static friction and hydraulic Hagen-Poiseuille resistance:

$$F_{extrusion} = F_{friction} + A_{barrel} \cdot \Delta P$$

Where, the pressure drop (ΔP) across the needle lumen is governed by:

$$\Delta P = (8 \cdot \eta \cdot L \cdot Q) / (\pi \cdot r4)$$

F extrusion= Total dynamic force required to propel the plunger.

F friction= Dynamic friction between the elastomeric stopper and the syringe barrel lumen.

A barrel= Cross-sectional inner area of the syringe barrel.

Delta P: Hydraulic pressure drops across the needle lumen.

Note: The Hagen–Poiseuille equation assumes Newtonian fluid behaviour; however, highly concentrated monoclonal antibody (mAb) formulations frequently exhibit shear-thinning (non-Newtonian) rheological behaviour under high shear rates."

Where η represents dynamic viscosity, L is needle length, Q is volumetric flow rate, and r is the internal needle radius. Crucially, required extrusion force scales inversely with the fourth power of the internal radius (r4); transitioning from a standard-walled 27G needle to a thin-walled 29G needle dramatically increases manual extrusion resistance [39].

5. MODERN APPLICATIONS & PATIENT-CENTRIC DELIVERY:

5.1. ON-BODY DELIVERY SYSTEMS: -

Stay attached to the body during drug administration.

Useful for large-volume or prolonged/controlled delivery, especially biologics.

Important factors: wearability, adhesion, accuracy, occlusion detection, drug stability, and patient comfort [40].

5.2 CONNECTED & REUSABLE DELIVERY SYSTEMS: -

Add electronic records, reminders, injection tracking, and real-time instructions.

Require attention to software, battery, cybersecurity, connectivity, and user safety [41].

5.3 SELF-ADMINISTRATION & PATIENT-CENTRIC DESIGN: -

Designed for easy and safe self-use by patients.

Consider handling, injection force, needle visibility, feedback, portability, storage, disposal, and complete-dose confirmation.

Devices should also be tested with real users in realistic conditions, not only in laboratories [42].

6. REGULATORY CONSIDERATION AND CHALLENGES:

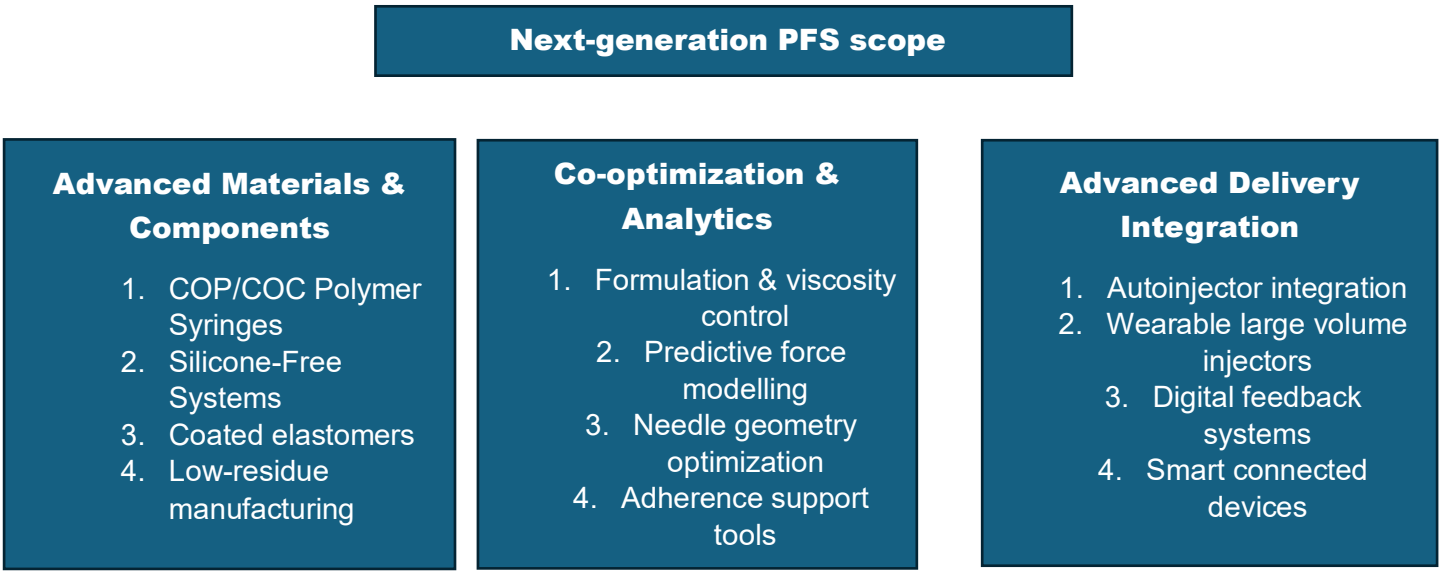
Prefilled syringes (PFS) function as integrated drug-device systems—often regulated as integral medicinal products, combination products, or medical devices depending on regional regulatory frameworks—requiring compliance with standards such as ISO 11040 and Medical Device Regulation (MDR) General Safety and Performance Requirements (GSPRs) alongside European Pharmacopoeia monographs and Notified Body Opinions where applicable. Because the syringe concurrently serves as a primary container-closure system and a delivery instrument,

manufacturers must implement risk management (ISO 14971/IEC 62366) and evaluate both drug-device compatibility and stability, specifically regarding sorption, precipitation, extractables, leachable, container-closure integrity, microbial safety, and simulated transport or worst-case stresses. Processing aids such as silicone oil present critical particulate-related risks, as released oil can nucleate the formation of proteinaceous particles or aggregates in biologic products. Advanced glass and plastic systems, plunger stoppers, and non-

compendial materials require thorough safety justifications, verified critical dimensions, and rigorous functional testing covering delivered-dose uniformity, glide force, needle penetration force, and activation force.

Throughout lifecycle management and development transitions, changes to device designs, drug volume, viscosity, intended use, or target populations necessitate bridging studies, risk assessments, and potential usability re-evaluations; meanwhile, evolving next-generation configurations (including dual-chamber designs, digital/electromechanical interfaces, and safety connectivity) highlight a growing need for early, flexible regulatory engagement to address emerging technologies that extend beyond existing guidelines [43,44].

7. FUTURE SCOPE:



8. CONCLUSIONS: -

Prefilled syringes (PFS) are integrated drug–device systems in which formulation, materials, device design, manufacturing, storage, and delivery must work together to ensure drug stability, safety, and accurate dosing. Glass is commonly used, while COP/COC polymers offer alternatives, especially for biologics. Major challenges include extractables/leachable, protein aggregation, particles, silicone interaction, and mechanical stress. Proper manufacturing, sterilization, storage, and transportation are essential. Future PFS development focuses on silicone-free/low-interaction materials, advanced lubrication, better particle control, and patient-centered designs to provide safer, reliable, and convenient injectable drug delivery.

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