Prefilled syringes are becoming an increasingly attractive option for complex biotechnology products, not least because of the savings in product volume compared to vials. There is now a wide range of options to suit different requirements which can make product selection a challenge. Wendy Saffell-Clemmer, Director of Research at Baxter Biopharma Solutions, looks at what advances are currently being made.

Expectations for growth in the prefilled syringe (PFS) market continue to be strong, and a recent report estimates that the global PFS market could reach a value of US$4.98 billion (£3.9 billion) in 2019. Drivers in the growth of PFS products include both the increase in injectable biologics in the development pipeline and globalisation (specifically, the expansion of PFS products into developing markets).

Prefilled syringes are particularly attractive to the developers of high-value, complex biotechnology products, such as monoclonal antibodies (mAbs) and fusion proteins. In contrast to vials, minimal overfill volume is needed to ensure delivery of the correct dose to the patient. The resulting savings in product volume required per batch may more than offset the increased cost of the PFS components.

The complex requirements of biologic products have driven innovation in PFS. While Type I glass remains the most common material for syringe barrels, new options in plastic syringes are gaining in popularity, including cyclic olefin polymer (COP), cyclic olefin copolymer (COC), polypropylene (PP), and polycarbonate (PC). In Japan today, 50% of syringes are plastic. Polymer syringes can be provided sterile and ready to fill, have the appearance of glass (Figure 1), and are resistant to breakage, making them preferable for highly potent drugs.

With the exception of the West Pharmaceutical Services Crystal Zenith COP syringe, most syringe barrels require the application of silicone oil to allow the plunger stopper to glide smoothly during use. In general, polymer syringes which do require silicone, such as BD’s Sterifill™, promote ultra-low silicone levels or, in the case of Schott’s TopPac SD®, utilise cross-linked silicone.

Reduction of silicone oil in syringe barrels is desirable for biotechnology products because silicone oil has been demonstrated to cause aggregation of a variety of proteins, and studies have demonstrated that the level of aggregation is proportional to the amount of silicone oil present.

During the manufacture of most glass syringe barrels, a tungsten probe is used to form the fluid path in the tip of the syringe, potentially leaving residual tungsten oxide vapour and tungsten particles. Soluble tungsten residue was determined to be the root cause of unusually high levels of aggregation in clinical trial batches of epoetin alfa and in an alpha helical protein formulation.
Syringe manufacturers have responded with PFS systems specifically designed for biotechnology products which have low specifications for tungsten residues, such as BD’s Hypak™ for Biotech glass syringe and BD’s Sterifill™ COP syringe. The Schott syriQ® Injente glass staked-needle syringe and West Pharma Crystal Zenith COP staked-needle syringe are both tungsten-free.

With options in barrel construction, silicone levels and tungsten levels, PFS selection has become complex. The use of newer PFS systems can increase costs, so careful evaluation of potential impact on product quality through laboratory studies should be conducted prior to final component selection to balance quality and cost to patients.

The risk management process in the ICH (International Conference on Harmonization) Q9, Quality Risk Management (Figure 2), can be applied to evaluation of drug formulation and PFS compatibility. The first step, risk identification, can be generalised for most peptide, protein and mAb products in a company’s pipeline. Suggested incompatibility risks for further consideration include 1) glass delamination, 2) sensitivity to tungsten and 3) aggregation resulting from silicone oil. The second step, risk analysis, can be accomplished with a review of the literature.

Glass delamination, or the flaking of glass particles from the interior surface of the container, has resulted in recalls of parenteral products in recent years. Glass delamination is not evident immediately and is usually observed in stability samples, particularly those at elevated temperatures. Formulation risk factors have been well documented and include a drug product pH ≥ 8.0, the presence of acetic acid, citrate and phosphate buffers, the presence of chelating agents such as EDTA, the presence of sodium salts of organic acid, and high concentrations of alkaline salts. Terminal sterilisation is also a risk, but is not applicable to biotechnology products.

The chemical composition of the glass and the production process, particularly formation and annealing, also impact risk of delamination. Factors such as heating rate, maximum temperature, and annealing time and temperature can all result in variations in glass durability.

The production process for PFS differs from vials, reducing the exposure of the product contact areas of the syringe barrel to extreme heat during the forming step. In a study comparing vials with PFS using a variety of formulation conditions, it was concluded that PFS “outperform vials for most test conditions and perform equivalently for the remaining”.

The presence of citrate or phosphate buffers was the formulation variable most likely to lead to an increase in released elements. No recalls or published reports of delamination in PFS have been reported indicating that it is not a significant risk. However, an assessment of formulation against known delamination risk factors is a best practice during container selection.

Suggested incompatibility risks for further formulation risk factors include 1) glass delamination, 2) sensitivity to tungsten and 3) aggregation resulting from silicone oil. The second step, risk analysis, can be accomplished with a review of the literature.

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The production process for PFS differs from vials, reducing the exposure of the product contact areas of the syringe barrel to extreme heat during the forming step. In a study comparing vials with PFS of an alpha helical protein formulation at pH 4.0 susceptible to tungsten-induced aggregation determined that the use of vacuum stoppering increases the amount of residual tungsten present in the solution. Vacuum stoppering removed the “air gap” typically present between the barrel funnel area and the product, exposing solution to the “tungsten rich” area of the syringe.

Studies of silicone oil-protein interactions have been conducted using spiked silicone oil in solution as well as by comparing solutions in siliconised syringes to non-siliconised syringes. A comprehensive study of the impact of formulation considerations on silicone oil-induced aggregation has not been completed, but some risk factors can be identified.

Silicone oil-induced aggregation is most likely to occur with high protein solutions, close to their solubility limit. In a study of abatacept, it was hypothesised that relatively high concentration of the protein may have solubilised or emulsified more oil from the surface than would have been the case with a lower concentration. In an anti-SEB mAb study of multiple formulations, the liquid in glass stoppers was visually clear at a pH close to the pI and after shaking. In studies of a model IgG1, the inclusion of 0.01% polysorbate 20 was found to inhibit silicone oil-induced aggregation during agitation. The study authors speculate that the surfactant “competes with the protein molecules for adsorption to the oil-water, air-water, and oil-air-water interfaces.” The same study demonstrated that sucrose partially inhibited silicone oil-induced aggregation.

One proposed theory for this effect is that sucrose increased the rate of silicone droplet formation, reducing the possible oil-water interfacial area, but further studies are needed to understand if sucrose has any effect on silicon oil-protein interactions.

Risk analysis for PFS container selection is summarised in Table 1. Following analysis of formulation risk factors, the process moves to risk evaluation. In formulations with multiple risk factors for glass delamination, experimental risk evaluation may not be value-added since extended stability would be required. In this case, or in the case of highly potent drugs where breakage could expose providers to hazards, a copolymer syringe should be considered.

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Protein sensitivity to tungsten can be evaluated through simple spiking studies. Risk evaluation for silicone oil-induced aggregation may be conducted by spiking formulations with a silicone oil-
Factors

Glass Delamination
Citrate, phosphate or acetate buffers pH ≥ 8.0
Chelating agents (ex. EDTA)
Sodium salts of organic acids
High concentration of alkaline salts

Tungsten Induced Aggregation
pH ≤ 7.0
Use of vacuum stoppering

Silicone Oil Induced Aggregation
High protein solutions
pH close to pI
Lack of surfactant

Table 1: Risk analysis for PFS selection.

“Evaluation of multiple lots of syringes is strongly recommended.”

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ABOUT THE AUTHOR

Wendy Saffell-Clemmer is the Director of the Baxter Biopharma Solutions R&D team. The team offers contract development services for small volume liquid (vial and syringe) and lyophilised products which are manufactured for external clients both at Baxter’s Bloomington, IN, US and Halle, Germany facilities.

Services include formulation development, lyophilisation cycle development, container compatibility and analytical development for small molecules, peptides, proteins, mAbs, ADCs and vaccines. Additionally the team performs analytical method validation, transfer and lifecycle maintenance for our QC group as well as cleaning validation method development and validation.

She volunteers as a member of the USP Expert Committee for Biological Analysis-General Chapters, the USP Expert Panel for Protein Measurement, and the AAPS Biosimilars Focus Group Steering Committee.