A RISK MANAGEMENT APPROACH TO PREFILLED SYRINGE SELECTION FOR BIOTECHNOLOGY PRODUCTS

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[1] 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).[2]

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.[3] 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).[3] In Japan today, 50% of syringes are plastic.[4] 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.

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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.[5]

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[6] and in an alpha helical protein formulation.[7]

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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® InJentle 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),[8] 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.[9] Glass delamination is not evident immediately and is usually observed in stability samples, particularly those at elevated temperatures.[10] Formulation risk factors have been well documented and include a drug product pH ≥8.0, the presence of acetate, 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.[11] 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".[12] 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.

Figure 1: (left to right) BD Sterifill™ COP, West Pharma Crystal Zenith COP, BD's Hypak™ Glass, and Schott TopPac® COC syringes.

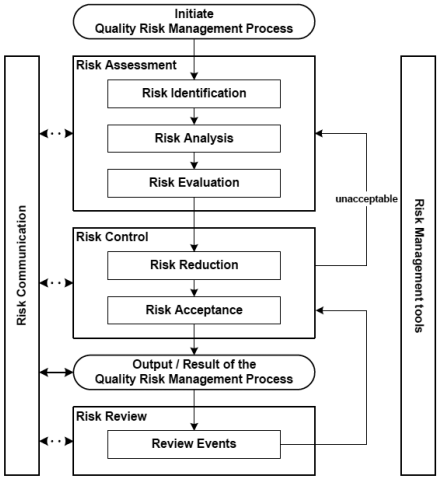


Figure 2: ICH Q9 risk management process.

Multiple incidences of tungsten-induced protein aggregation have been reported. A study of precipitation of a mAb by tungsten demonstrated rapid coagulation by tungsten polyanions at pH 5.0, but concluded a lower risk for proteins formulated at pH >6.0 since higher pH prevents formation of tungsten polyanions.[13] However, in a study of Epoetin in a buffered solution at pH 7.0 spiked with tungsten pin extract, small amounts of aggregates were detected after storage for six months at 25°C.[6] A study 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.[7] 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,[14] 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 effect was only seen at a pH close to the pI and after shaking.[14] 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".[15] The same study demonstrated that sucrose partially inhibited silicone oil-induced aggregation.

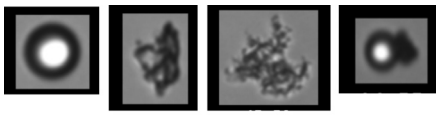
One proposed theory for this effect is that sucrose increased the rate of silicone droplet formation, reducing the possible oil-water interfacial area, but further studies are needed to understand if sucrose has any effect on silicon oil-protein interactions.

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.

Protein sensitivity to tungsten can be evaluated through simple spiking studies.[16] Risk evaluation for silicone oil-induced aggregation may be conducted by spiking formulations with a silicone oil-

Identified Risk	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.



a. b. c. d.

Figure 3: Images of a) silicone oil droplet b) protein aggregate c) protein aggregate d) possible protein aggregate bound to silicone oil captured using flow imaging.

water emulsion and subjecting samples to aggregation. A detailed experimental study is described by Badkar.[17] Many of the studies referenced were published prior to the wide adoption of flow imaging technology. Flow imaging provides both particle counts as well as an assessment of the morphology of a particle. Powerful software allows for the sorting of particles based on their shape. Silicone oil droplets, in particular, may be similar to protein particles and will result in high <10 µm particle counts in all spiked samples. However, silicone oil droplets have a characteristic spherical shape and appearance with a light centre and increasing contrast towards the exterior of the sphere (Figure 3), which allows standard flow imaging software systems to identify and subtract silicone oil particles.[18] Flow imaging can also identify protein aggregates bound to silicone oil droplets.

Following risk evaluation using solution spiking studies, risk reduction can be performed through selection of syringe characteristics such as ultra-low silicone, cross-linked silicone or silicone-free products. A small, accelerated stability study, using hand-filled syringes, is recommended prior to making a final selection. Samples should be stored at standard and accelerated conditions, and exposed to aggregation stress.

"Evaluation of multiple lots of syringes is strongly recommended."

For biotechnology products, at minimum, flow imaging and product stability-indicating test methods should be used to evaluate the formation of subvisible aggregates and assess product stability. Additionally, the accelerated stability study is an opportunity to ensure that the function of the syringe, specifically the peak glide force, is unchanged by the product and is suitable for patient needs or the requirements of a planned auto-injector system.

Evaluation of multiple lots of syringes is strongly recommended. In internal, non-published studies, significant differences in the number of silicone oil-related particles have been observed using flow imaging in different lots of the same PFS. Extractables/leachables studies should be initiated at the selection of the preferred container closure. The risk management process (Figure 4) concludes with selection of the PFS, acceptance of risk, and development of product test methods and specifications. Continued monitoring through regular product batch testing and a strong supplier relationship for notification and assessment of any syringe manufacturing changes is essential to maintaining product quality.

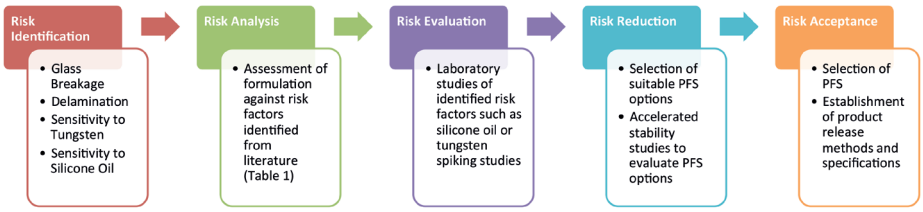


Figure 4: Risk management process applied to PFS container selection for a biologic product.

The complex requirements of biologic products have driven innovation in prefilled syringe technology, which has resulted in a wide array of options for selection by the product development team. While new syringe options may increase cost for the final product, evaluation of risks of specific formulation instability and component incompatibility should be conducted to balance quality, safety and cost. ICH Q9 Quality Risk Management provides a framework which can be applied to create an efficient process for PFS container selection.

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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.

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