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AN INNOVATIVE SOLUTION TO ADDRESS SILICONE-RELATED CONCERNS

In this piece, Christian Herget, Worldwide Strategic Marketing Leader Biotech, BD Medical – Pharmaceutical Systems, explores the potential impacts of silicone coatings on prefilled syringe-based injectable biopharmaceutical combination products and recent advances at BD to reduce these impacts.

Injectable biopharmaceuticals are a pivotal element in the arsenal of treatments for chronic diseases like multiple sclerosis and rheumatoid arthritis [1] and, as with all therapeutics administered regularly over long periods of time, efficacy and safety are particularly critical to ensuring consistent quality of care. However, biopharmaceuticals are highly complex and, consequently, vulnerable to several forms of degradation [2] that can have an impact on their efficacy and safety.

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Because of their protein structure,[2] biopharmaceutical formulations must be parenterally administered; many are injected. With prefilled syringes – the packaging of choice for many biopharmaceuticals – pharma companies must grapple with new challenges like interactions between the container (i.e. the syringes) and drug [1] that could affect drug efficacy and safety and, in the event of undesirable reactions, lengthen time to market or compromise safety and efficacy of the drug.

For biopharmaceuticals packaged in prefilled syringes, this adds a new challenge: the syringe, now part of the product,[3] has the potential to compromise the drug inside. A number of syringe attributes must be carefully assessed to ensure that the drug will not interact in any unexpected ways with its primary container. Therefore, choosing the right syringe is now one of the key factors to consider in order to avoid costly development delays or, worse, potential product recalls.[1]

The prefillable syringes available on the market are not always completely suitable for biopharmaceuticals and several of their common components – like the silicone oil used as a lubricant to ensure smooth plunger action with lower injection force [4] – have been evaluated and deemed potentially incompatible with biopharmaceuticals.

BD draws upon decades of collaboration with pharma industry leaders and understands the importance of satisfying the most

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stringent efficacy, safety and quality criteria to provide patients with innovative injectable therapies while helping pharmaceutical companies mitigate product development and commercialisation risks.

SILICONE & BIOPHARMACEUTICALS: WHAT YOU SHOULD KNOW

A number of concerns have been raised about silicone, used as a prefilled syringe lubricant and possible interactions with biopharmaceutical drugs:[1,5]

- Cosmetic: sub-visible (SbVPs) and visible particles may compromise drug purity verification, resulting in increased false rejects and higher total cost of ownership
- Pharmaceutical: potential loss of therapeutic response and changes in activity that could affect drug safety, efficacy and quality
- Technical: aggressive formulations can affect the syringe's gliding properties, leading to incomplete injection with auto injectors and, in some cases, product recalls
- Clinical: according to some research, and under specific experimental conditions, silicone SbVPs could promote aggregation or co-aggregation of biopharmaceuticals. Such aggregates are suspected potentially to play a role in unwanted immune responses leading to the production of anti-drug antibodies (ADAs). ADAs may bind to therapeutic proteins molecules reducing their therapeutic efficacy by neutralising their activity and/or increasing their rates of clearance.[6]

Some manufacturers have introduced syringes equipped with baked silicone and non-siliconised plastic syringes as a potential solution to these challenges.[7,8,9] However, baked silicone technology is generally not compatible with staked needle design, the gold standard for injectable biopharmaceuticals. Furthermore, baked silicone only partially reduces silicone-induced SbVPs.

Plastic prefilled syringe technology has a limited track record for injectable biopharmaceuticals and introduces a whole new set of inherent challenges and risks – such as drug compatibility and manufacturability – that pharmaceutical companies need to control. BD is addressing silicone-related issues with innovative technologies to reduce silicone-induced SbVPs to their lowest ever levels, based on well characterised chemistry of silicone lubricant and therefore supplementary challenges and risks, while retaining the time and force required for injection, known as syringeability [4] – a key factor in patient compliance with auto injected drug regimens – and auto-injector functionality, as well as managing change control risk.

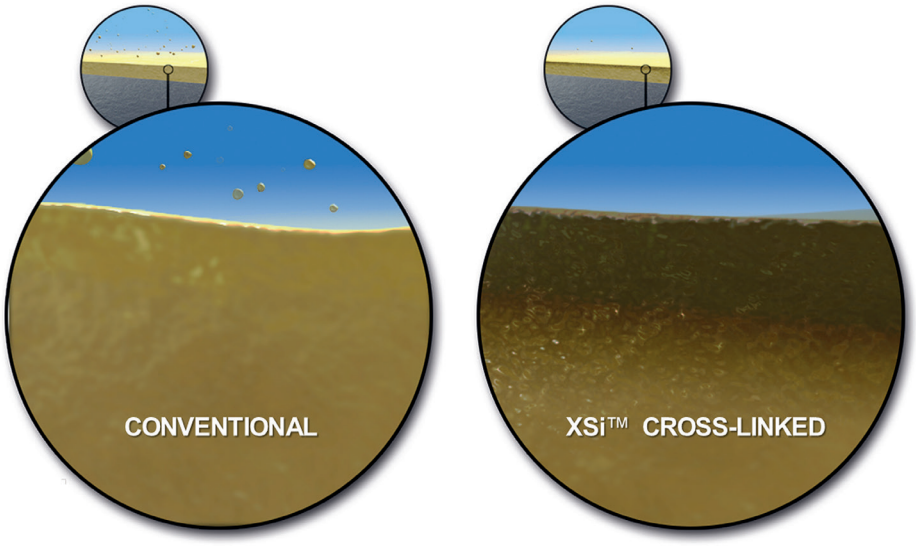

Figure 1: Conventional versus BD XSi™ cross-linked silicone chain networking. The modified lubricant layer acts as a barrier to silicone emulsification, reducing the migration of silicone oil from the barrel and maintaining the lubricity required for the syringe to perform as intended.

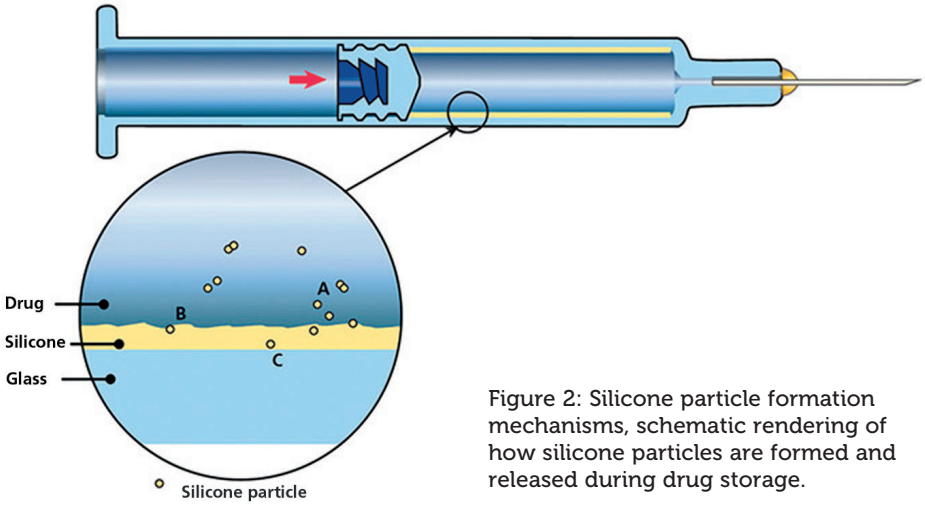

Figure 2: Silicone particle formation mechanisms, schematic rendering of how silicone particles are formed and released during drug storage.

REDUCING SbVPs WITHOUT COMPROMISING PERFORMANCE

The emergence of biopharmaceuticals and the associated combination product development challenges [3] have made silicone a topic of discussion in the prefilled syringe market. BD responded with the BD XSi™ research programme to develop a staked needle prefillable syringe that ensures full auto injector compatibility and that significantly reduces potential risks associated with sub-visible silicone particles.

The programme resulted in an innovative immobilised silicone coating: cross-linked silicone BD XSi™, shown in Figure 1. This coating reduces the risks associated with sub-visible silicone particles while retaining lubrication performance; in addition, BD XSi™ is based on established chemistry of silicone lubricant, for rapid implementation of the prefilled syringe format for both legacy and pipeline drugs.[1]

BD XSi™ technology ensures container and lubricant layer inertness, resistance to degradation by drug product, biological drug stability, full gliding performance and the low silicone-derived SbVPs comparable with levels of non-siliconised prefilled syringes and better than baked silicone. A more robust lubricant layer also offers added benefits for innovative, more aggressive, drug

formulations aiming to increase payload.

BD XSi™ technology is ready for adoption with no alteration to existing prefillable syringe manufacturing or filling processes. In addition to its strategic benefits, BD XSi™ exhibits overall container performance that is equal or superior to conventional delivery systems.[1] Designed for staked needle syringes and used with conventional stoppers, the BD XSi™ proprietary coating employs an advanced, well-characterised and unique silicone based technology that minimises the risks and facilitates adoption.

PARTICLE FORMATION MECHANISMS & DETECTION

Gathering data is a fundamental prerequisite to assessing the performance of any new technology, and silicone prefillable syringe coatings are no exception. But first we must understand the mechanisms that cause the formation of silicone-induced SbVPs.

As their name indicates, silicone-induced SbVPs in prefilled syringes originate from the silicone lubricant applied to the inner syringe surface. There are three SbVP groups, each with its own formation mechanisms and potential impacts. The three significant populations of silicone-induced SbVPs present in a prefilled syringe format are:

Type A: silicone droplets released (or emulsified) into the drug solution soon after filling and therefore in contact with the drug solution throughout the entire product shelf-life; could potentially form silicone-protein complexes.

Type B: Silicone particles from the silicone surface that remains in contact with the drug solution throughout the product shelf-life and that could move into solution at some point in time.

Type C: Silicone particles from the bulk silicone layer sloughed off the wall during injection. In contact with the drug for a much shorter time than the other particle types, these nevertheless represent a significant portion of the particles measured using current compendial methods.

SbVP detection is constantly improving, thanks to new analytical techniques.[5] Particles smaller than 10 µm – and potentially into the submicron range – are now detectable. We can now also determine the types of these tiny particles. This more detailed data will greatly enhance SbVP monitoring and, ultimately, provide a deeper understanding of the contribution of silicone oil to the overall pool of detected SbVPs. This will contribute to accelerating the industry's discussion of silicone oil and PFSs and drive the emergence of solutions to reduce SbVP formation and impacts.

MEASURING SbVP REDUCTION

Our study [1] looked at commercially available prefillable glass syringes with no silicone coating, a conventional sprayed-on silicone coating, baked silicone coating and the BD XSi™ cross-linked silicone coating. We used reflectometry, optical microscopy, and time-of-flight secondary ion mass spectrometry to measure particle content in a model buffer system (polysorbate 80/phosphate-buffered saline: PS80/PBS).

Our findings show that the syringes with the BD XSi™ cross-linked silicone coating outperformed syringes with a conventional sprayed-on silicone coating, and baked silicon coating (see Figure 3). Enhanced integrity of the lubricant coating led to significantly fewer SbVPs in the liquid formulations, particularly after agitation stresses introduced by shipping of the syringes. The BD XSi™ coating also maintained the syringes' intended functional properties as determined by high-performance size-exclusion chromatography.

ASSESSING PRODUCT PERFORMANCE OVER TIME

Our BD XSi™ study also assessed two critical syringe properties that indicate product performance over time: the integrity of the BD XSi™ coating layer after incubation with the drug and syringeability, manifested by the time and force required for injection.

Coating integrity over time and syringeability [4] are increasingly important in the development of innovative biopharmaceuticals packaged in prefilled syringes. The formulations of these drugs are enhanced to increase the dose of active pharmaceutical ingredient (API) to achieve better patient outcomes and/or extend injection intervals. These enhancements may cause degradation of the lubricant layer during drug storage. This degradation can lead to SbVP release, of course. However, it can also compromise drug syringeability and thus jeopardise the flawless drug delivery of the combination

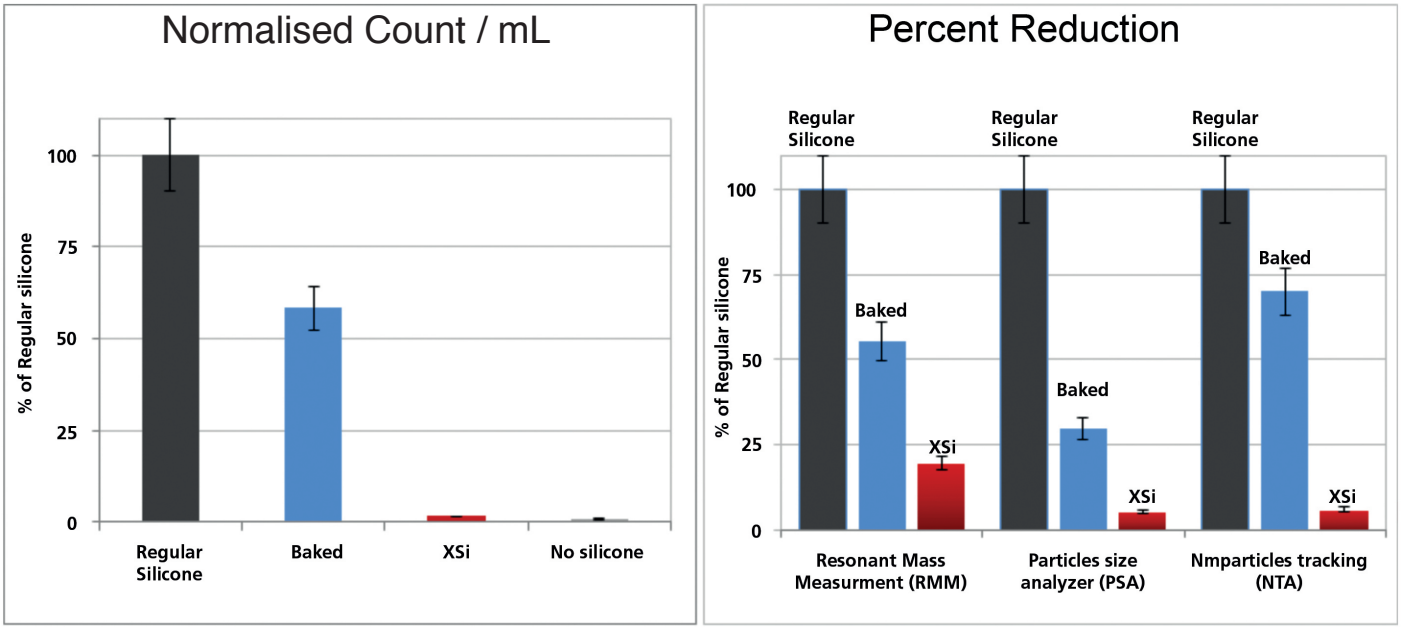

Figure 3: Silicone SbVPs released after agitation of PS80 solutions in PBS from various PFS.

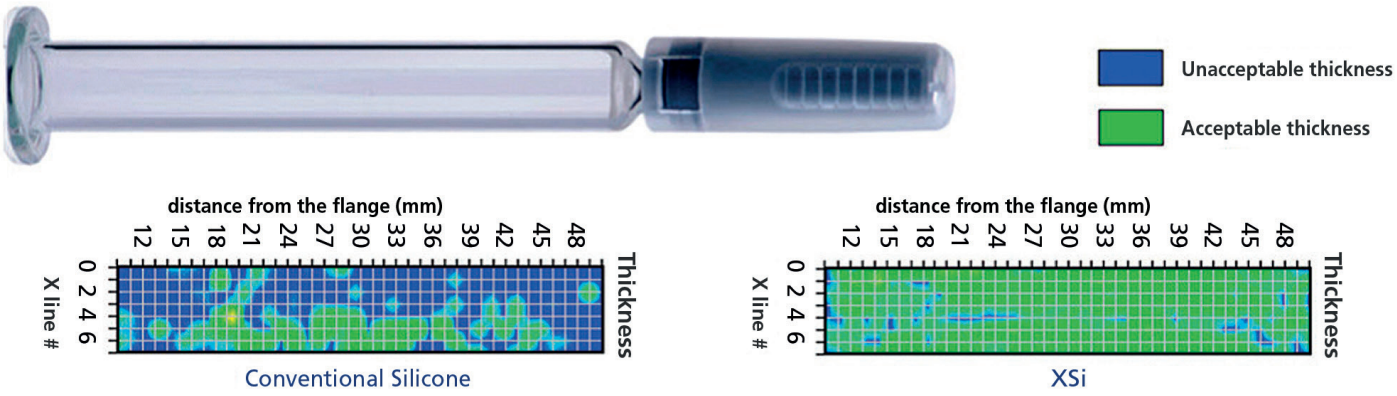

Figure 4: Layer integrity after drug contact. Thickness of coating measured in distance from flange using reflectometry.

product. If identified during product development, these types of issues can lengthen time to market. BD XSi TM reduces degradation and therefore can help minimise the risk of development delays due to undesired drug-container interactions.

For auto injectors and attached needles, BD XSi™ provided the expected lubricious behaviour with a similar level of functional gliding performance as conventional siliconised syringes. This syringeability is widely accepted as a factor in patient compliance with auto-injected drug regimens.

We also looked at the integrity of the BD XSi™ coating after drug contact. We used shelf-life testing designed to mimic realistic but extremely stringent conditions on placebo-filled prefilled syringes with the BD XSi™ coating. BD XSi™ demonstrated exceptional stability over time, retaining its critical quality attributes of density, chemical composition and dimension even after storage in contact with a drug.

CONCLUSION

Biopharmaceuticals are revolutionising care. However, innovations are needed to make sure the promise of biopharmaceuticals is fulfilled, especially for patients with chronic diseases where drug safety and efficacy are particularly crucial. Prefilled syringes have emerged as the delivery system of choice for biopharmaceuticals, but several challenges must be overcome to ensure the ultimate safety and efficacy of syringe-based combination products.

Container-drug interactions are one such challenge, and silicone syringe linings are facing particular scrutiny. BD has made silicone a priority R&D topic, and is making advances in product engineering materials and characterisation tools that show positive results in meeting and overcoming these challenges.

Innovative products like BD XSi™ have been shown to reduce silicone-induced SbVPs to the lowest extent ever, minimising the risk of undesired drug-container interactions with optimised drug delivery performance. And, because BD XSi™ is based on conventional chemistry of silicone lubricant, it delivers the full spectrum of benefits of high-end staked needle prefillable syringes, while minimising the complexity, risks and costs of the development and commercialisation of innovative combination products.

BD XSi™ is just one product in BD's range of solutions for biotech. BD draws on a long track-record of customer-centric innovation and real-world problem solving to develop innovative products and services to support pharmaceutical companies' product development and lifecycle management strategies. From the BD Neopak™ top-of-the-line glass PFS system to BD VisioGuard™ inspected stoppers, BD is a trusted partner for biopharmaceuticals, helping pharmaceutical companies reduce time to market, improve in operational efficiency and create competitive advantage by gaining the preference of patients and prescribers.

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