When BD launched its first glass prefilla-
table syringe into the market in 1954, the syringes
primarily were used for drug delivery by health
care workers in a clinical setting. Since then, the
dynamics of health care delivery have changed
drastically. In particular, biotech drugs (biologics)
have revolutionised care for a variety of chronic
diseases. By 2018, six of the top 20 – and seven
of the top eight – leading drugs in the US by
sales will be biologics. With the expansion of
biologics in chronic disease care, administration
of treatment continues to evolve from the tradi-
tional model of clinician-administered care to a
model based on self-administration by educated
and empowered patients. Subsequently, demand
has grown for safe, easy-to-use, and convenient
delivery devices, such as auto-injectors, pens, and
patch injectors.

The biotechnology market and US FDA set
very specific requirements for drug delivery of
biologics, which have unique properties and
consist of large molecules that may be sensitive
to interaction with components of the delivery
device, such as the syringe lining. Prefilled
syringes and auto-injectors, in which biologics are
commonly packaged, facilitate patient self-care
and are regulated under the FDA’s Final Rule on
Combination Products, issued in January of this
year, that clarifies how earlier requirements are
to be applied. The FDA scrutinises the quality
of product components (including sensitivity of
drugs to tungsten, silicone, adhesives, and rubber)
and the integration of combination products. Phar-
maceutical companies also demand a drive
to lower total cost of ownership, platform stan-
ardisation, and risk-mitigation strategies, such as
dual sourcing, to mitigate supply-associated risk
for containers and devices.

These changes have transformed the market
for delivery devices to meet the demands of
clinicians, patients, pharmaceutical companies,
and regulatory agencies for simple, efficient,
and safe drug administration. In order to meet
these increasing demands, drug delivery device
suppliers must continue to innovate to address
product quality, cost savings, and risk mitiga-
tion. BD has a proven commitment to continued
innovation in the biotech space.

INTRODUCTION TO PREFILLED
SYRINGES

As many biologics cannot be taken orally,
the role of injection devices should grow along
with the expansion of biologics in patient care,
making the choice of drug delivery system
increasingly important. Prefilled syringes offer
numerous benefits for patients and treatment
administration, including efficiency in terms of
time, reduction in medication risk due to dosing
errors or cross-contamination, and elimination
of the need to measure doses and prepare, fill,
and clean syringes. These benefits have
led to increased market demand for prefilled
syringes to administer a variety of drugs appro-
priate for patient self-care, including biologics.

INTRODUCTION
Patients express preference for drug delivery devices that are convenient to use (with strong preferences for auto-injectors), and for more comfortable injections, with less pain and shorter injection times. Another preference, for less frequent injection, while primarily related to the molecule being injected, may be influenced by the capabilities of the delivery device. In their design, prefilled syringes address these patient concerns. In fact, patients prefer prefilled syringes over other options, which have been shown to improve adherence with self-administered treatments.6

With increased use of prefilled syringes, regulatory agencies have significantly increased their expectations for the individual components and combined device. Prefilled syringes and auto-injectors generally fall under regulation for combination products and require a system-based approach.14

Rigor must be demonstrated in developing and providing data regarding the compatibility of the components of the device as well as compatibility of the drug and container.11 Human factors, such as patient age, visual impairment, or limited dexterity may affect accurate drug delivery, and their assessment is required for all delivery devices.14

Given these trends, it is increasingly important that drug formulation and delivery strategies be integrated at an early stage in the development of complex biologics. Issues with poor integration of prefilled syringes in auto-injectors have led to recalls and complaints, and can be avoided when compatible design is a priority from inception through delivery.

**DRUG-CONTAINER COMPATIBILITY**

There is a potential for unwanted interactions between biologics and other substances with which they come into contact, which is an issue with implications for the design of prefilled syringes.11 Silicone is commonly used to lubricate the inner wall of syringes and facilitate smooth injection. An area of intense interest is the development of subvisible particles (SVPs) of silicone in drug solution.13

FDA’s Container Closure Guidance and SVP Guidance note the potential impact of SVPs and offer strategies for monitoring their presence.5

Silicone-induced SVPs arise from interactions between the lubricant and active contents of prefilled syringes. They may be released into the drug (1) immediately or shortly after filling, (2) over time during storage, or (3) only during the injection process itself. The first and second categories are most problematic, as these particles remain in contact with the drug for prolonged periods of time and have the potential to form silicone-protein complexes or otherwise affect the drug. However, in glass prefilled syringes, a given amount of silicone is needed for injector functionality, limiting the degree to which silicone can be eliminated, and use of plastic syringes without silicone lubrication is not widely accepted.9

Recently, surface cross-linking of silicone has been proposed as a solution for silicone-induced SVP reduction without negative effects on performance.7 BD’s XSi™ cross-linked silicone technology has brought this solution to market and been demonstrated to reduce silicone-induced SVPs significantly while ensuring auto-injector functionality with an appropriate glide force (see Figure 1). Compared with conventional silicone coating, maximum glide force with the XSi™ coating is increased by a minimal 5-10% (Figure 2).11 While introducing little or no SVPs, syringes using the XSi™ coating provide the expected lubrication and level of glide performance. This latter feature, known as syringeability, has been shown to affect patient’s adherence with self-injected therapies.9

XSi™ technology is inert, resists drug degrada-
tion, provides biologic drug stability, produc-
es little or no SVPs, and does not significantly increase glide force. Importantly, in providing these benefits, the XSi™ technology introduces no new chemistry or chemical substrates during the manufacturing process, thus reducing the regulatory hurdle for review and registration.6

**PATIENT INTERFACE/ FUNCTIONALITY**

Clinicians factor in ease of administration, convenience, and comfort when making treatment decisions, while patients seek fewer injections and optimised injection comfort (minimised pain and injection time).2 Designs that integrate prefilled syringes with an auto-injector must take into account components such as spring force, needle gauge, and flange strength, all of which contribute to the patient’s injection experience.

Closely linked with innovation in biologics is a trend toward higher-viscosity drug formulations because of the size of the molecules, concentrations needed for effective response, and the practical limitations of subcutaneous injection (for example, volume).11,12,13

Molecule size and concentration are relatively fixed qualities, making innovation in delivery necessary. One approach is the use of large-volume solutions, including 2.25 ml syringes and patch injectors, such as the BD Microinfuser™ patch injectors. Once the formulation for a self-injected drug is set, the inner diameter of the needle strongly influences the glide force necessary for injection.5 New needle technologies present another opportunity for innovation. Good examples are the BD HyFlow™ and BD Physiolis™ needles. BD HyFlow™ is a 27-gauge needle that uses special thin-wall technology, resulting in a larger inner diameter that allows greater flow of drug without substantially increasing the
The FDA issued specific regulatory guidance to address SVPs and acceptable quality level standards that must be met with regard to assessing the potential for interaction between the product intended for the syringe and the syringe itself. New chemistry introduced to drug containers warrants new FDA submissions, whereas innovations in existing chemistry avoid the need for additional review. Long before the advent of biologics, silicone has been used in prefilled syringes to facilitate smooth gliding of the plunger and stopper. In the biologics era, prefilled syringes represent the current standard for drug administration, but concerns about interactions between silicone syringe linings and silicone-induced SVPs have surfaced. Syringes using XSi™ technology reduce drug-silicone interactions and SVPs to the lowest possible level, are designed to be fully compatible with autoinjectors, and do not introduce new chemicals or chemistry.

CONCLUSION

Biologic agents continue to revolutionise patient care. Innovation to improve the patient experience of administering biologics will help fulfil the promise of these agents in the treatment of chronic illness. Although prefilled syringes make injection of biologics safer and more efficient, there remain several challenges to be overcome. These include developing technology designed to address the unique characteristics of biologics, such as their higher viscosity and potential to interact with silicone syringe linings. BD has made advances in product engineering and materials that show positive results in meeting and overcoming these challenges with innovative products such as BD XSi™, BD HyFlow™, and BD Neopak™.

REFERENCES

11. BD Data on File.
14. BD Data on File.
15. BD Data on File.
Precision in every direction

Introducing our new standard in product quality and supporting services enabling you to reach higher levels of robustness and convenience