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BREAKING THE 1 ML BARRIER

This article, from Christian Herget, Worldwide Strategic Marketing Leader, Biotech, and Vincent Herin, R&D Staff Engineer, both of BD Medical-Pharmaceutical Systems, explores the evolution of innovative syringe-based combination products for the administration of biopharmaceutical drugs. Particular focus is placed on the increased interest in reducing the number of required injections in order to enhance patient safety and comfort. Often this can only be achieved by increasing the volume of each injection. However, to consider a subcutaneous injection of more than 1 mL as a possible design target, one has to establish the technical feasibility, safety and patient tolerability of larger-volume delivery options.

With more than 900 biologics under development,[1] biopharmaceuticals play a growing role in the treatment of a broad range of conditions. Their potential market is expected to reach US$278 billion (£190 billion) by 2020.[2] Due to their sensitive nature, biopharmaceuticals must be administered parenterally.[3]

Prefilled syringes (PFS) have emerged as one of the delivery systems of choice for biopharmaceuticals.[4] Unlike vials, which require a 20% overfill, PFS help reduce costs and drug wastage.[5] They contribute to improving dosing accuracy as well as patient convenience and safety, which results in enhanced patient quality of life.[5] However, the development of drug products, and in particular sensitive biologics[4] in PFS, creates a unique set of challenges (Figure 1). It is necessary to ensure the safety, efficacy, cost effectiveness and flawless operation of such syringe-based combination products.

One such challenge includes undesired container-drug interactions[6] which can cause drug degradation as well as protein or particulate aggregation of sensitive biologics.[4] To ensure a drug will not interact in unexpected ways with its primary container, a number of syringe attributes must be carefully assessed.

PFS for biologics like the BD Neopak™ (Figure 2) have been specifically optimised to minimise risks reducing tungsten level or improving the leachable and extractable profiles from the used elastomers and glue.[2] If not addressed, such factors can lead to development setbacks, unnecessarily high manufacturing costs and even failure of the combination products in the field.[4] This may jeopardise ambitious time-to-market goals, increase total cost of ownership, or lower patient and prescriber preferences – and, as a result, threaten the overall success of the project.

> "Conventional wisdom suggests that SC injections are limited to a maximum volume of 1 mL. However, there is a lack of evidence to fully support or contradict this belief.[9]"

To maximise chances of success, the development of syringe-based injectables should start with the definition of a target product profile. Leveraging the experience and expertise of container and device partners is also essential.

Based on experience gained during multiple co-development programs, BD has continuously worked to advance

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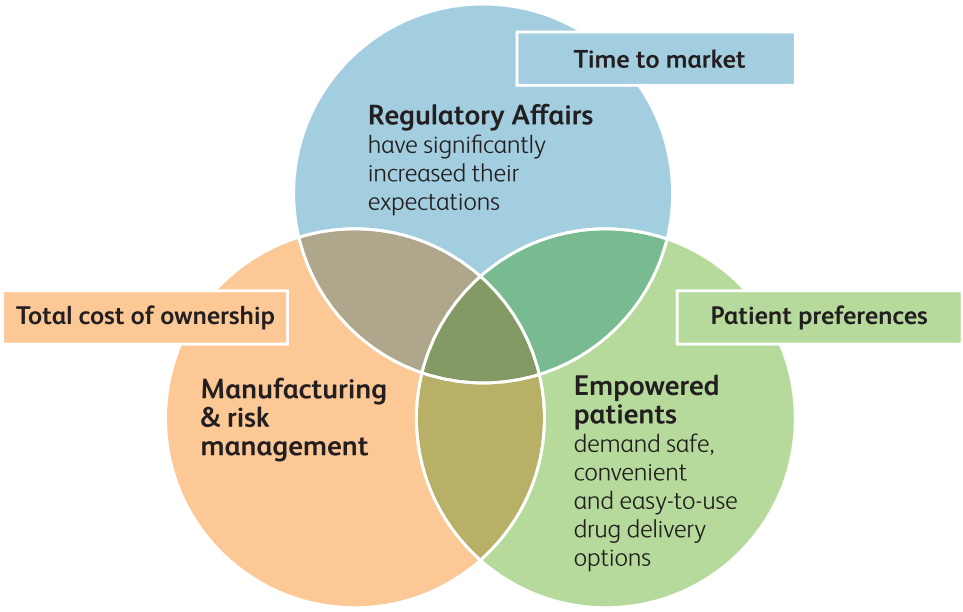

Figure 1: Challenges faced by pharmaceutical companies.

the design and performance of PFS for biopharmaceuticals to address these challenges.

With BD Neopak™, BD has followed a quality-by-design approach to create a new PFS that aims to achieve ppm quality levels. The product is manufactured using a fully indexed process. This eliminates glass-to-glass contact and produces fewer visual defects.[2] The result is lower rejection rates during visual inspection in the customers' production line and increased glass strength.[2] BD Neopak™ features reduced silicone levels while maintaining the low break-loose and gliding performance required for autoinjectors. By limiting dimensional tolerances and putting dead volume space under control, the BD Neopak™ glass prefillable syringe reduces drug wastage and overfilling, thus lowering the total cost of ownership.

CHALLENGES OF LARGE-VOLUME HIGH-VISCOSITY INJECTABLES

Medical device companies are faced with new challenges. Throughout the pharmaceutical industry, the emerging trend is to reduce the number of injected doses. The primary causes of this trend include the desire to reduce the frequency of injections.[7] Various solutions have been explored to achieve this goal. For example, it is possible to optimise the pharmacokinetic properties of a drug by increasing the concentration or PEGylation of the API to create a longer acting drug. However, this approach does not always yield the desired result and eventually leads to the need for increased injection volumes.[8]

Conventional wisdom suggests that SC injections are limited to a maximum volume of 1 mL. However, there is a lack of evidence to fully support or contradict this belief.[9] If the clinical development of an injectable indicates that the target dose exceeds 1 mL and a syringe-based SC injection is the route of administration of choice, then a number of key questions must be answered. Before exploring the design of injectables with large volumes, we must analyse various factors such as technical feasibility, safety, tolerability and end user-related human factor aspects.

Figure 2: BD Neopak™ 2.25 mL glass prefillable syringe for large-volume injection.

FEASIBILITY, SAFETY AND TOLERABILITY OF LARGE-VOLUME INJECTIONS

Gathering robust clinical evidence on the feasibility, safety and tolerability of large-volume SC injections is a prerequisite for the development of any therapy that could use such injections. In partnership with a leading biopharmaceutical company, BD has performed a study to evaluate the impact of large-volume placebo injectables using a combination of various fluid viscosities and flow rates in order to analyse pain tolerability, feasibility and safety.[10]

In the single-centre, comparative, randomised, crossover Phase I study, 24 healthy adults each received six injections of either a 2 or 3 mL placebo solution in the abdomen area, with three fluid viscosities (1, 8-10, and 15-20 cP), and two injection flow rates (0.02 and 0.3 mL/s, the latter being comparable with the injection speed of autoinjectors).

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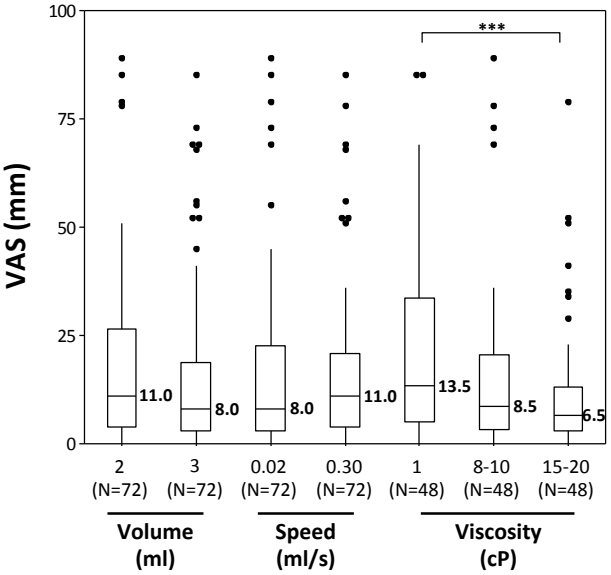
During the study, various factors were evaluated to determine the feasibility, safety and tolerability of the injections. Pain was evaluated via a 100 mm visual analogue scale (VAS - 0 mm/no pain, 100 mm/extreme pain). The injected volume was calculated by subtracting the residual



Results grouped according to volume, flow speed and viscosity. A Visual Analogue Scale (VAS) was used to assess pain with a range of 0-mm/no pain to 100-mm/extreme pain. Medians are indicated. A significant difference was observed across the three levels of viscosity (*** p .0003) (1).10

Figure 3: Perceived: injection pain after 144 injections.

> The BD UltraSafe™ Plus Passive Needle Guard 2.25 mL not only delivers the intended safety function, but also extends available design space for combination products. Its user-friendly ergonomics enable the delivery of fluids with greater viscosity."

volume in the syringe. The local injection reaction was assessed by recording signs of bleeding, erythema, swelling and haematoma formation. Reactions were checked immediately and approximately 15±5 minutes after the injection. The location of injected fluid in body tissues was assessed by ultrasonography.

During the study, no severe reactions were recorded for local bleeding, erythema and haematoma. In two of the 144 injections (1.4%), swelling/induration was considered severe immediately after the injection but became moderate 15 minutes later; both cases were observed in the 3 mL group with a fast injection flow rate. The results (see Figure 3) indicated that relatively large-volume SC injections of viscous solutions can be performed in a safe manner.

Despite widespread belief that the upper limit for SC injections is approximately 1 mL, this exploratory study suggests that injections up to 3 mL in the abdomen area are in fact well tolerated regardless of injection flow rate and fluid viscosity.

The study demonstrated that the volume of an injection did not have a statistically significant impact on perceived pain. Injections up to 3 mL were well tolerated when carried out with a flow rate typical for autoinjectors and with solutions of elevated viscosity (e.g. 15-20 cP).

USABILITY OF CONTAINER-DEVICE COMBINATIONS FOR LARGER VOLUMES

After establishing that higher volumes than 1 mL can be safely injected subcutaneously and such injections are well tolerated by the patients, another key question to address is whether such injections can be properly performed by the end users.

To demonstrate that the BD Neopak™ 2.25 mL syringes can be used as intended by representative end users, a human factors study was carried out asking participants to inject solution of various viscosities using BD Neopak™ 2.25 mL alone, equipped with backstop or combined with BD UltraSafe™ Plus Passive Needle Guard 2.25 mL. This device was developed in parallel to BD Neopak™ 2.25 mL as a solution to comply with needle safety regulation. Apart from reducing the risk of needlestick injuries, these devices are strongly preferred by end users compared with naked syringes.[2]

Study results[2] highlight that BD Neopak™ 2.25 mL allows the injection of a solution with low viscosity (defined as 1cP in the study) with a success rate of 100%.

Injections of a solution with medium viscosity (defined as 10 cP in the study) with BD Neopak™ 2.25 mL alone were successfully achieved by the vast majority of participants. The success rate could be increased to 100% by using BD Neopak™ 2.25 mL equipped with a backstop or combined with BD UltraSafe™ Plus Passive Needle Guard 2.25 mL, enabling all participants to perform the injection properly.

Asked to inject a highly viscous solution (defined as 30 cP in the study), the vast majority of participants were able to perform the task successfully using BD Neopak™ 2.25 mL equipped with a backstop. By using BD Neopak™ 2.25 mL combined with BD UltraSafe™ Plus Passive Needle Guard 2.25 mL, all participants were able to complete the high viscosity injection.

This finding highlights that the BD UltraSafe™ Plus Passive Needle Guard 2.25 mL not only delivers the intended safety function, but also extends available design space for combination products. Its user-friendly ergonomics enable the delivery of fluids with greater viscosity.

By applying a system approach to the development of the primary container and secondary devices and accessories, BD assesses and maps the design space, helps to ensure container and device compatibility as well as system performance.

As a result, biopharmaceutical manufacturers benefit from lower risks in terms of setbacks or delays during combination product development.

CONCLUSION

Combining PFS and secondary devices is an increasingly popular option to differentiate drugs with relatively similar patient outcomes. In this case, product differentiation is not solely based on the safety and efficacy of the drug but instead on the overall experience relating to the administration.[11]

Choosing the right partner for combination product development is critical to achieve favourable outcomes in terms of time to market, total cost of ownership, and patient or prescriber preferences. BD understands that meeting customers' complex and evolving needs requires extensive consultation throughout the entire process from development to commercialisation. To meet this demand, BD has developed its capacities to deliver support every step of the way.

Thanks to BD Neopak™ 2.25 mL and BD UltraSafe™ Plus Passive Needle Guard 2.25 mL, BD has developed an innovative solution to deliver large-volume, high-viscosity biopharmaceuticals. These products address the need to reduce the frequency of injections while enhancing the safety and comfort of chronic-disease patients.[12]

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BD Neopak™ 2.25 mL

Glass prefillable syringe for large-volume injection

Designed to address your large-volume injection challenges

BD Neopak™ 2.25 mL has been developed to protect and deliver injectable biologics that require subcutaneous injection with volumes of up to 2 mL. Engineered with chronic-disease patients in mind, it opens the way for the development of safer, more comfortable therapies with reduced injection frequency.

Built on the legacy of BD's most advanced biotech platform, **BD Neopak™ 2.25 mL** follows a quality-by-design approach developed to achieve Six-Sigma quality levels. Dare to break the 1 mL barrier – leverage **BD Neopak™ 2.25 mL** to develop therapies that make a difference.

Contact us to find out about other innovative solutions for biotech drugs:

- **BD UltraSafe Plus™ Passive Needle Guard*** is designed for one-handed passive activation and to support viscous drug delivery. It offers a broad range of branding options, including colors and extended add-on flanges.
- **BD Durashield™** glass strengthening technology is designed to address glass breakage concerns.
- **BD Neopak™ XSi™** is designed to significantly reduce sub-visible silicone particles and stabilize the lubrifying layer.**
- **BD Visioguard™** vision inspection technology for stoppers is designed to reduce contamination and defects.**

**A 2.25 mL BD UltraSafe Plus™ Passive Needle Guard is currently under development*
*** BD data on file*

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