HOW SHORTER NEEDLES WITH THINNER WALLS ARE SET TO IMPROVE THE INJECTION EXPERIENCE IN CHRONIC CARE

Aurélie Pager, Clinical and Human Factors Program Leader; Brigitte Duinat, Senior Engineer; and Barbara Alves, Regulatory Affairs Specialist, all of BD Medical – Pharmaceutical Systems, reporting on several patient studies, look at how new BD Neopak™ XtraFlow™ prefillable glass-based syringes with shorter, 8 mm needles and thinner wall cannula technology are set to improve the injection experience for subcutaneous drug delivery in chronic care.

For decades, the most commonly used needle length for subcutaneous chronic drug delivery has been half an inch (12.7 mm).[1] As a result, most secondary injection devices have been developed around 12.7 mm staked needle prefillable syringes (PFSs) and the exposed needle length for manual injection has remained mainly focused around 12.7 mm.

However, there is a proportion of self-injecting patients who do not apply[2] the recommended subcutaneous injection technique (45° with or without skin pinch, 90° with skin pinch),[3] thereby increasing the risk profile of accidental intramuscular injection when using needles of this length. Therefore, the 12.7 mm needle length may not be optimal for subcutaneous drug delivery.

State-of-the-art innovation processes[4] have evolved and are now more centred on end users' needs (patients, healthcare workers and lay caregivers) rather than on developing new products around existing constraints. Additionally, needle length and, most importantly, needle inner diameter are key parameters influencing injection force for a given injection time and solution viscosity.[1] Reducing the injection force required to deliver solutions by manual injection is a parameter influencing patient preference, especially when high viscosities are injected.[2]

Leveraging findings in the diabetes care space, where there have been a series of innovations including reducing exposed needle lengths,[5] BD Medical – Pharmaceutical Systems is launching BD Neopak™ XtraFlow™* – a prefillable glass-based syringe solution featuring an 8 mm needle with thinner wall cannula technology. Enabling the transition from the 12.7 mm needle length towards shorter 8 mm needles, in combination with thinner wall needle technology to reduce pressure drop and enhance flow,[6] can provide improved PFS solutions for subcutaneous drug delivery both for end users in chronic care settings and for pharmaceutical companies.

The BD Neopak™ XtraFlow™ syringe is set to improve subcutaneous drug delivery and the injection experience through three main benefits: by allowing the possibility of delivering higher drug viscosities and/or volumes without compromising the end user experience through substantial reduction of injection effort or time;[2,6,7] by increasing the chances of targeting the right tissue even if the recommended injection technique is not applied,[8] thereby supporting the efficacy of manually administered chronic therapies; and by potentially reducing patients' needle-related anxiety.[2]

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In the remainder of this article, we will present several frequently asked questions from BD pharma partners, split into three groups according to each of our areas of expertise.

The questions cover research and design mindset applied to the development of the BD Neopak™ XtraFlow™ solution, and how the anticipated clinical benefits of 8 mm needles[9] will support their broad adoption over time for subcutaneous drug delivery, particularly for use in chronic care settings.

The Importance of Human Factors Evidence – Aurélie Pager (AP)

Q What did BD identify as priority areas of improvement for chronic subcutaneous drug delivery and how is BD Neopak™ XtraFlow™ set to address these?

AP A recent market research study[10] allowed us to identify three main areas of priority:

1. Enabling subcutaneous bolus delivery of high viscosity and higher volume drugs (up to 2 mL) without compromising the end-user experience
2. Reducing the risk of accidental intramuscular (IM) injections
3. Reducing needle-related anxiety and pain perception.

> "We aim to enable the injection of high drug viscosities without increasing injection force."

By addressing these areas, we believe we can contribute to improving the patient experience[2,7] and that of all end users.

The development of the BD Neopak™ XtraFlow™ prefillable syringe with 8 mm, thinner-wall needle technology is an important next step for the treatment of chronic diseases in addition to diabetes, where there has been a decades-long trend in reducing needle lengths for drug delivery.[5] We saw this trend in diabetes care where, due to clinical relevance,[9] shorter needles largely and successfully replaced 12.7 mm needles which had previously been the *de facto* needle length, based on industry convention rather than on clinical directive.

This shift to shorter needles occurred due to concerns about patient safety, as insulin absorption into muscles could lead to hypoglycaemic episodes.[11] While increased safety for a similar efficacy was the most important outcome of the move to shorter needles in the diabetes treatment space,[9,11] another key finding was that shorter needles also significantly reduced needle-related anxiety and perceived pain,[12] which led to a substantial increase in patient comfort.[13]

With the introduction of the 8 mm BD Neopak™ XtraFlow™ needle, we aim to enable the injection of high drug viscosities without increasing injection force[6] for other chronic disease treatments, given the range of injection volumes and viscosities that exist.[1] The BD Neopak™ XtraFlow™ syringe is designed to enable an acceptable injection force[6] or an acceptable holding time (e.g. up to 10 seconds for 1 mL injections)[14,15,16] when delivering higher drug viscosities and volumes. Needle length and, most importantly, needle inner diameter are dominant factors influencing injection force for the same injection time and a determined viscosity, based on our calculations derived from the Bernouilli – Poiseuille equations simulating fluid and pressure drop (Figure 1).[6]

Q The BD Neopak™ XtraFlow™ prefillable syringe enables a tangible reduction in injection force. How was this determined and perceived by end users?

AP When combined with thinner-wall technology, such as with ultra-thin wall (UTW) needles, BD Neopak™ XtraFlow™ enables a reduced injection force or injection time required to push on the plunger rod to deliver the

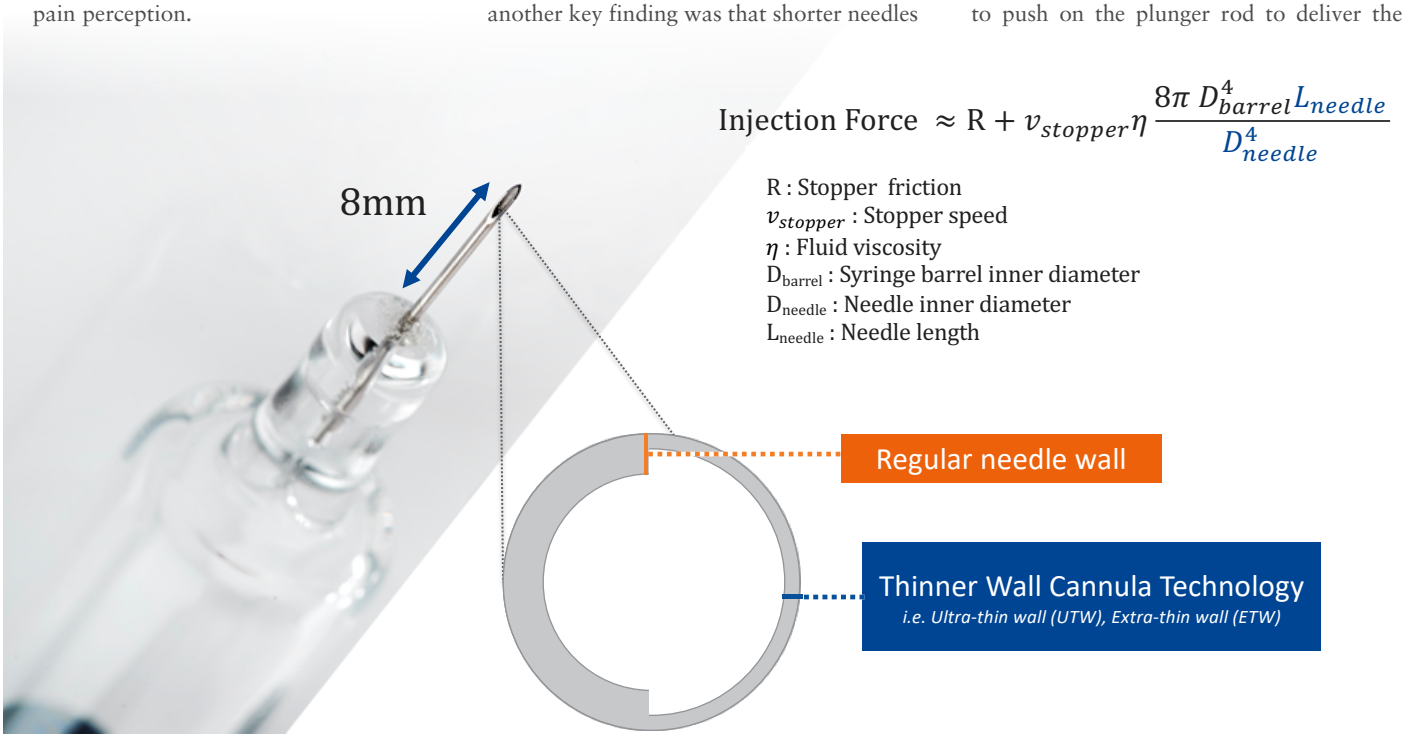

Figure 1: The BD Neopak™ XtraFlow™ glass prefillable syringe platform with staked 8 mm needle and thinner wall cannula technology options. Injection force equation (top right), derived from the Bernouilli – Poiseuille equations, can be used for fluid and pressure drop simulations, respectively.[6] This equation illustrates how the needle inner diameter and, to a lesser extent, needle length, influence the injection force for a given injection time and solution viscosity. (Negligible terms simplified in the equation.)

"There can be significant deviation from recommended subcutaneous injection techniques, even for experienced users."

injectable.[6] With patients increasingly taking on the responsibility of self-injecting, they may want less frequent dosing schedules.[17] This means that drug delivery systems must be capable of delivering higher volumes and/or higher viscosities.[1,17]

Improving the patient injection experience was one of the key objectives in the development of the BD Neopak™ XtraFlow™. BD's expertise and experience in needle manufacturing and needle wall technology allowed us to adjust needle length and wall thickness to increase fluid flow, while introducing minimal change from an industrial, PFS fill and finish process perspective.

For example, when compared with 27G special-thin wall (STW) 12.7 mm needles, BD Neopak™ XtraFlow™, with the combination of 27G UTW and 8 mm needle length, reduces injection force by ~46% at a viscosity of 30 cP and by ~34% at a viscosity of 10 cP for a similar injection time, according to a mathematical modelling simulation.[6] These differences in force were shown to be perceptible to end users in recent human factors studies.[2,7]

Indeed, a 2019 BD human factors study showed that over 50% of chronic disease patients, including both naïve and experienced self-injecting patients, have a preference for the BD Neopak™ XtraFlow™ syringe over commonly used syringes. They attributed the main reason for their preference to the reduction of injection force, with the second most-cited reason being the shorter needle length.[2] BD intends to share these results in a future peer-reviewed publication.

Q What evidence supports the notion that BD Neopak™ XtraFlow™ helps target the correct tissue, assisting in the proper delivery of subcutaneous injections?

AP Similarly to the enhancements achieved in the diabetes space, we expect that the 8 mm BD Neopak™ XtraFlow™ will increase the chances of targeting the subcutaneous tissue, even if the recommended injection technique is not performed correctly,[8] and it may reduce patient needle-related anxiety – thus potentially improving the overall patient self-injection experience.[2,7]

Self-injecting is never an easy task for patients, even for those with years of experience. In the same human factors study, we saw that there can be significant deviation from recommended subcutaneous injection techniques, even for experienced users.[2] In our study, patients used the non-recommended injection technique of 90° injection angle with no skin pinch 35% of the time. With commonly used 12.7 mm needles, and when the recommended injection technique is not followed or is done incorrectly (no skin pinch or an incorrectly done one), we estimate this will increase the risk of injecting into the intramuscular (IM) tissue.

By adopting a shorter, 8 mm needle, our simulations[8] show that the risk of accidental IM injections could be reduced at both the abdominal and thigh injection sites between two and eight times, without increasing the risk of accidental intradermal (ID) injections, considering both 90° and 45° injection angles, without skin pinch. This reduction was derived from a mathematical model based on a study assessing human skin layer thickness at various injection sites, conducted among 388 adults (of various ages, genders, ethnicities and body mass index scores).[5] This potential reduced risk of IM injection applies to all types of patients, including at-risk populations such as children and lean adults who have less subcutaneous fat.[18]

The BD human factors study cited earlier allowed us to assess the injection techniques used and thus three different user groups were represented: "naïve" participants, "experienced" participants, and participants "experienced but with hand impairment" (e.g. patients diagnosed with rheumatoid arthritis or multiple sclerosis). For those with hand impairment, following recommended injection techniques can be consistently challenging.

"The risk of accidental IM injections could be reduced at both the abdominal and thigh injection sites."

This subpopulation showed a rate of non-recommended injection technique at 90°, without skin pinch, three times more often than when compared with non-hand-impaired, experienced patients. The highest rate of injection error was observed in the naïve patient population.[2] The 8 mm needle length of BD Neopak™ XtraFlow™ could reduce accidental IM injection for all patients performing non-recommended injection techniques, as discussed previously.[8] BD Neopak™ XtraFlow™ also provides the possibility of reducing the pressure required to deliver drug therapies and facilitate self-injection, especially for users with hand dexterity issues.[2,7]

Q How did you substantiate the positive impact that BD Neopak™ XtraFlow™ has on patients' needle-related anxiety?

AP Over the last 20 years, a number of scientific studies in the diabetes care space have established that needle-related anxiety and perceived pain can be reduced with shorter and thinner needles. For example, in 1999, Ross *et al*[19] evaluated both visible 8 mm (30G) needles and 12.7 mm needles in diabetes treatment on a number of parameters, including pain perception. The subjects using 8 mm needles reported less perceived pain than those using 12.7 mm needles.

Bergenstal *et al* (2015)[11] subsequently reported diabetic patient evaluations favouring short needles in terms of pain, ease of use and overall patient preference.** In addition to peer-reviewed articles, BD's innovations in diabetes care contributed to our understanding of the relationship between needle length, needle diameter and the patient experience in the context of chronic diabetes care.

For the development of the BD Neopak™ XtraFlow™, the abovementioned human factors study evaluated patient use of syringes, needle-related anxiety, ease of use, acceptance and preference, compared with commonly used 12.7mm 27G STW needles.

In this study,[2] we looked at needle-related anxiety in patients suffering from chronic diseases. The study population included both naïve and experienced self-injecting participants. Prior to any simulation, two uncapped syringes with visible needles were presented to the naïve participants to assess their anxiety level. The results show that the BD Neopak™ XtraFlow™ syringe (8 mm 27G UTW)

was rated as less anxiety-inducing than a similar-looking syringe which had a longer needle (12.7 mm 27G STW).

After the simulated injections, the experienced participants were asked if they usually felt anxiety when self-injecting with either PFS or syringe and vial treatments. It is noteworthy that over 40% of these participants still feel anxious, even after many years of self-injecting. Additionally, nearly all experienced participants saw advantages to the shorter needle length of the BD Neopak™ XtraFlow™. Indeed, they found it less intimidating, eliciting the impression that it would be less painful and more comfortable to use than the 12.7 mm needle.

Q **Secondary delivery systems are increasingly being adopted to help end-users in chronic care to deliver higher viscosity or high-volume therapies. How does BD Neopak™ XtraFlow™ impact the injection experience with such delivery systems?**

AP We recently tested the benefits of the BD UltraSafe PLUS™* 2.25 mL safety system in combination with the BD Neopak™ XtraFlow™ in a human factors validation study.[7] The user groups included in this study were healthcare professionals, and both naïve and experienced self-injection patients, with and without hand impairment. The study shows that, with a commonly used 12.7 mm 27G needle, the system is usable and test subjects express confidence that the system will indeed protect them from needlestick injuries.

However, when tested with a viscous 30 cP solution, a perceptible reduction in injection force is provided when combined with BD Neopak™ XtraFlow™. More than 120 injection simulations were performed in this study, with the rate of operational difficulties observed during the simulated injections being lower with BD Neopak™ XtraFlow™ than with other, commonly used syringes. Users also perceived a reduction in the force needed to push the plunger during injection.

Indeed, the percentage of users who rated the plunger as "easy or very easy to push" increased by up to five times across all user groups. BD UltraSafe PLUS™ 2.25 mL, when combined with BD Neopak™ XtraFlow™, may provide a better experience for end users, including self-injecting patients, with and without hand impairment.

Needle Robustness and Systems Expertise – Brigitte Duinat (BD)

Q **How would BD Neopak™ XtraFlow™ and its thinner needle wall configuration perform with regards to needle mechanical resistance?**

BD A key driver in the development of BD Neopak™ XtraFlow™ was to keep needle mechanical properties comparable to currently marketed needles (i.e. 12.7 mm 29G thin wall and 27G special-thin wall needles) to support acceptable resistance to bending and buckling. Calculations performed through well-established mechanical laws included estimations of resistance to bending and buckling.[20]*** These figures indicate needle mechanical resistance when challenged with a perpendicular or axial force until it reaches plastic deformation.

Resistance to bending and buckling for different BD Neopak™ XtraFlow™ configurations, including the 8 mm 27G UTW and the 8 mm 29G extra-thin wall (ETW) configurations, demonstrated equivalent, and sometimes even superior, mechanical resistance when compared with those of 12.7 mm 29G thin wall, commonly used needles. Our study shows that combining shorter needle length with thinner needle wall technology maintains, and may even improve, needle mechanical resistance to bending and buckling.[20]

Q **What is BD's integrated system solutions approach and what is its role in the design of new needle technologies?**

BD Our partnership with biopharmaceutical companies for the past 30 years has taught us that developing and launching drug-device combination products is a long and expensive journey for pharmaceutical companies and their partners. BD is well positioned to support the development efforts and success of our pharmaceutical partners through more robust, better-designed system solutions, using our history with and experience in combination products.[21,22]

For combination products, not only is it necessary to have excellent compatibility between the drug and the PFS primary container, but there is also a growing need to secure system integration with a safety device or an autoinjector. Such complex systems increase the number of functional interfaces and thus introduce several challenges,[23,24] particularly when these systems are sourced from multiple vendors. BD is able to manage all the requirements, from the delivery of system requirement definitions to sub-system, component and manufacturing process requirements.

Moreover, our capabilities cover all design control aspects, including usability (human factors) engineering, and preclinical and clinical evaluation. BD Neopak™ XtraFlow™ syringes, which will soon expand our solution portfolio for chronic drug delivery, will benefit from robust integration with BD injection devices, including the BD Intevia* 2.25 mL large-volume autoinjector and BD UltraSafe PLUS™ safety devices.

Regulatory Considerations When Adopting New Needle Technologies – Barbara Alves (BA)

Q **Are there any specific challenges regarding the registration of a drug device combination including a syringe with a shorter, 8mm needle and an enlarged inner diameter, such as with the BD Neopak™ XtraFlow™?**

BA There is no change in the type of regulatory submission needed with the BD Neopak™ XtraFlow™ compared with a BD glass prefillable syringe with a commonly used 12.7 mm needle. BD Neopak™ XtraFlow™ is part of a combination product in the US and is also part of an integral drug device combination (DDC) in Europe, including a drug and syringe only or additional devices such as a needlestick injury prevention accessory or an autoinjector.****

According to Article 117 of the European Medical Device Regulation, the integral DDC has to be assessed first by an MDR-accredited notified body, who should focus on the safety and performance of the device part of the DDC. (The latest official date for implementation of European Medical Device Regulations, article 117, was May

"There is no change in the type of regulatory submission needed with the BD Neopak™ XtraFlow™ compared with a BD glass prefillable syringe with a commonly used 12.7 mm needle."

26th, 2020, though this is expected to be extended by one year following the vote on an amendment by the European Parliament on April 17th, 2020.)

The applicable General Safety and Performance Requirements (GSPR), Annex I of the EU MDR are part of the design input specifications of BD Neopak™ XtraFlow™, which means that BD will provide supportive evidence of safety and performance to its biopharmaceutical partners to help them build their own GSPR packages for the DDC. BD Neopak™ XtraFlow™ will be included in our existing glass syringe drug master file type III in the US, meaning no change for drug combination product registration in that country.

It is interesting to note that there is no requirement, specific standard or guidance that recommends needle length for subcutaneous injections and that health authorities have already approved 8 mm needle devices, including PFSs.

Q If a biopharmaceutical company has already started its clinical program with a 12.7 mm staked needle PFS, would switching to an 8 mm needle still be possible and, if so, what would that switch entail?

BA Health authorities recommend using the final marketing presentation for Phase III clinical studies; in cases where this is not feasible, the same authorities recommend an appropriate bridging strategy.[25,26] From a clinical point of view, the 8 mm needle length has been demonstrated[11] to reach the targeted subcutaneous tissue when recommended injection techniques are maintained. However, even if the injection would occur in the same targeted tissue with 8 mm and 12.7 mm needles, which would mitigate the risk of finding different drug pharmacokinetic/pharmacodynamic (PK/PD) results, a bridging study with 8 mm needles may be required to leverage initial clinical data generated by a PFS with a 12.7 mm needle.

FDA draft guidance on bridging for drug-device and biologic-device combination products describes the potential impact of changes in needle penetration depth and rate of delivery on bioavailability PK/PD.[26] This is also the reason why bridging PK/PD studies are often needed when pharmaceutical companies introduce autoinjector presentations, even if no PFS change is involved. One simple way to introduce a PFS with an 8 mm needle would be to leverage the required bridging study for autoinjectors and complement it with an additional study arm for manual use.

A revealing example of this would be in the context of diabetes pen needles, where clinical studies are performed to support changes in needle length and/or gauge, with a focus on glucose control and leakage at the injection site, to determine the potential impact on glycaemia levels.[11] While those data were a requirement for development and approval of some pen needles, they are mostly informative for future product development and for supporting clinical decisions, including being used as a foundation for clinical practice guidelines.

> "BD Neopak™ XtraFlow™ technology provides a combination of staked-needle length, gauge and inner diameter that enhances the user experience[2] and helps patients comfortably and successfully perform their subcutaneous self-injections."

CONCLUSION

Improving the patient injection experience should be considered a priority, especially for patients with chronic conditions who must inject themselves frequently over an extended period of time.

BD Neopak™ XtraFlow™ technology provides a combination of staked-needle length, gauge and inner diameter that enhances the user experience[2] and helps patients comfortably and successfully perform their subcutaneous self-injections. This is particularly relevant for patients with reduced hand dexterity[7] and when injecting higher viscosity and/or higher volume therapies.[7] What's more, BD Neopak™ XtraFlow™ offers a platform that can be applied to manual injection, safety device and autoinjector applications.

With the benefits and evidence presented in this article and, more specifically, with their contribution to enhancing the patient self-injection experience,[2,7] there appears to be no reason to delay the transition to shorter, thinner-wall needles for therapies that require subcutaneous injection, especially for chronic diseases.

Complementing its large portfolio of delivery solutions for chronic injectable drugs, BD Medical – Pharmaceutical Systems will also soon be integrating BD Neopak™ XtraFlow™ syringes into both BD UltraSafe PLUS™ safety devices for the prevention of needlestick injuries and into the BD Intevia™ 2.25 mL autoinjector platform, with the intention of even further enhancing the patient injection experience.

** BD Neopak™ XtraFlow™, BD UltraSafe PLUS™ 2.25 mL and BD Intevia™ 2.25 mL are products under development; some statements are forward looking and are subject to a variety of risks and uncertainties.*
*** Bergenstal et al compared 4 mm (32G), 8 mm (31G) and 12.7 mm (29G) needles and found no statistically significant difference in preference between 4 mm or 8 mm pen needles, in the case of diabetes care.*
**** Based on mathematical modeling. Bench, preclinical and clinical testing not performed.*
***** According to US FDA 21 CFR part 3.2(e) in and EU MDR 2017/745 article 1(9).*

ABOUT THE COMPANY

BD is a large, diverse, global medical technology company. Its Medical Pharmaceutical Systems division is the world's largest syringe manufacturer. It offers prefillable syringes, self-injection systems, safety and shielding solutions, and needle technologies and associated pharma services.

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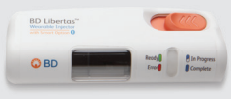

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