User experience improvement in manual self-injection of viscous solutions with 8mm ultra-thin wall needles (BD Neopak™ XtraFlow™*)

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Background

BD identified three main areas of improvement regarding self-injection in the biologic drug space for the treatment of chronic diseases.[1]

PHARMA PRIORITIES[1]

- Enabling the delivery of high viscosity/volume drugs in the subcutaneous tissue without degrading end-user experience through substantial reduction of injection effort and/or time (for patients, caregivers or health care workers[2])
- Reducing the risk of injecting accidentally into intramuscular (IM) tissue, without increasing the risk of injecting into intradermal (ID) tissue
- Reducing needle-related anxiety and injection-related pain perception (during manual injection)

Methods

- Human Factors study
- Voice of the customer market research
- Mathematical models
  $F_{ejection} = F_{gliding} + F_{fluid}$
- Peer-reviewed articles

A formative Human Factors/usability engineering study was conducted to compare the user experience between two prefillable syringes, the marketed BD Neopak™ syringe versus the BD Neopak™ XtraFlow™ syringe in development. Usability, ease of use, anxiety, acceptance and preference of the two syringes were assessed by self-injecting naïve and experienced chronic disease patients (with or without moderate hand impairment).

BD conducted market research among 90 stakeholders in various pharmaceutical companies, asking them to assess and prioritize unmet needs associated with parenteral administration of biologic drugs for chronic treatments.
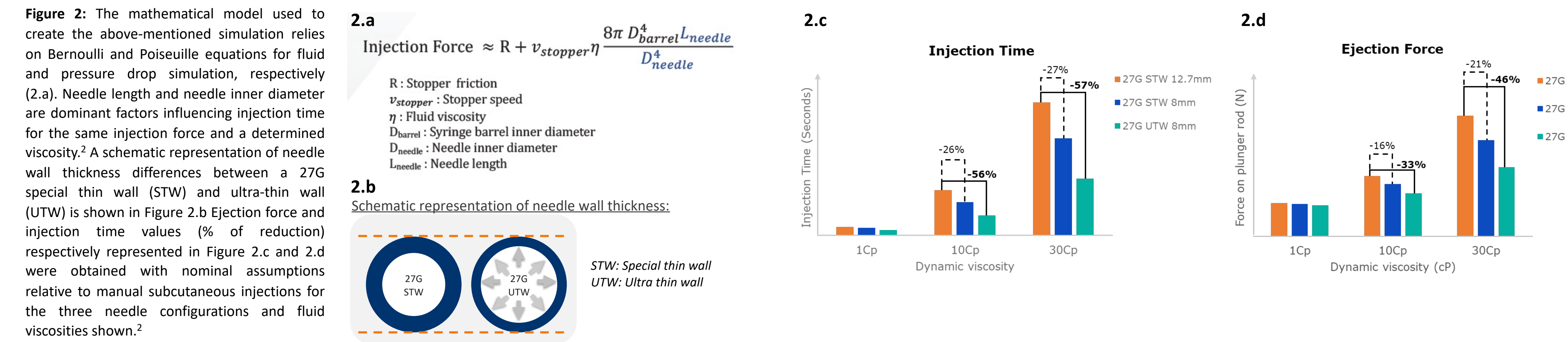
Mathematical simulation model was conducted with inputs of subcutaneous injection parameters impacting pressure drop, based on the Hagen Poiseuille equation, to assess the theoretical contribution of needle parameters to solution delivery.
Mathematical model of predictability regarding risk to inject in the muscle instead of the subcutaneous tissue at 90° or 45° without skin pinch with various needle lengths

Articles were reviewed (mainly in diabetes care space) describing the benefits of short needles, including their clinical impact and acceptability. Studies included various patient populations, injection sites and needle configurations.

Results

Injection time or ejection force required to push on the plunger rod for viscous solution delivery (10-30Cp) is reduced by up to 57% with BD Neopak™ XtraFlow™ 27G 8mm ultra-thin wall when compared to the BD Neopak™ 12.7mm 27G special-thin wall syringe[2]

Ejection force and injection time values were simulated through a mathematical model based on the Hagen-Poiseuille equation to assess the theoretical contribution of needle parameters to syringe-based subcutaneous solution delivery.[2] When combined with thinner-wall technology, such as UTW needles, BD Neopak™ XtraFlow™ enables a reduction in injection force (Figure 2c.) or injection time (Figure 2d.) required to deliver the 2mL solution when compared with a 27G STW 12.7mm needle syringe.[2,3]

Figure 2: The mathematical model used to create the above-mentioned simulation relies on Bernoulli and Poiseuille equations for fluid and pressure drop simulation, respectively (2.a). Needle length and needle inner diameter are dominant factors influencing injection time for the same injection force and a determined viscosity.[2] A schematic representation of needle wall thickness differences between a 27G special thin wall (STW) and ultra-thin wall (UTW) is shown in Figure 2.b Ejection force and injection time values (% of reduction) respectively represented in Figure 2.c and 2.d were obtained with nominal assumptions relative to manual subcutaneous injections for the three needle configurations and fluid viscosities shown.[2]

2.a
$$Injection\ Force \approx R + v_{stopper} \frac{8\pi\ D_{barrel}^4 L_{needle}}{D_{needle}^4}$$

R : Stopper friction
$v_{stopper}$: Stopper speed
η : Fluid viscosity
D_{barrel} : Syringe barrel inner diameter
D_{needle} : Needle inner diameter
L_{needle} : Needle length

2.b Schematic representation of needle wall thickness:
27G STW   27G UTW
STW: Special thin wall
UTW: Ultra thin wall

2.c Injection Time
2.d Ejection Force

Human Factors study shows that median injection time is reduced by up to 50% with Neopak™ Xtraflow™ 8mm UTW syringe compared to Neopak™ 12.7mm STW syringe[4]

A Human Factors formative study was conducted by BD in 2019 on different groups of chronic disease patients. Subcutaneous injections with two syringe configurations were simulated using foam pad and injection time was measured using a stopwatch (standard deviation of 1 to 2 sec).[4]
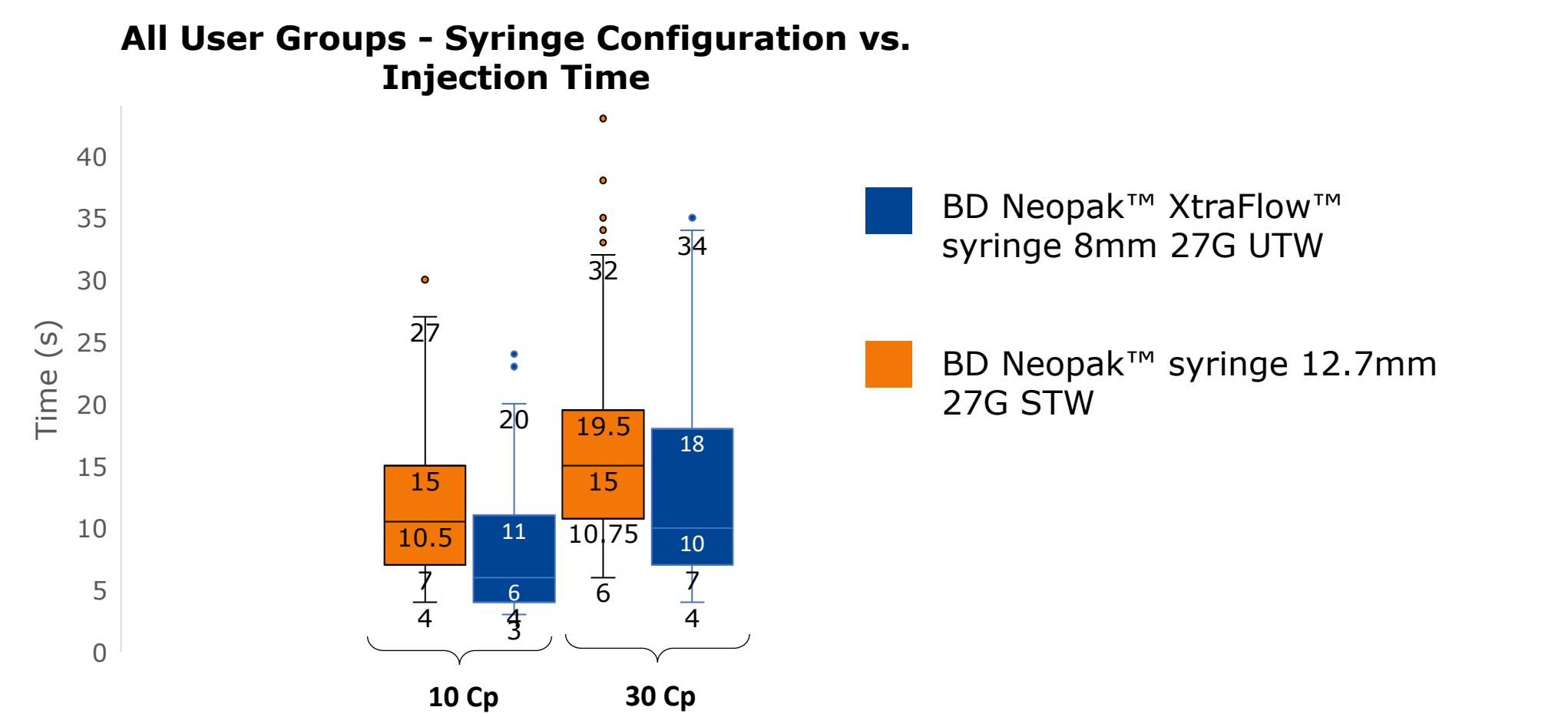

All User Groups - Syringe Configuration vs. Injection Time
- BD Neopak™ XtraFlow™ syringe 8mm 27G UTW
- BD Neopak™ syringe 12.7mm 27G STW

Figure 3: The Human Factors study results show that the median injection times for simulations performed with the BD Neopak™ XtraFlow™ 27G 8mm UTW syringes were reduced compared to those with the BD Neopak™ 12.7mm STW syringe whatever the viscosity considered.[4] When performing an injection, the patient uses an injection force that will lead to a certain injection time. For instance, if a participant uses a same injection force to perform injections with the two syringes, the injection time with the BD Neopak™ XtraFlow™ 8mm UTW syringe will be reduced by up to 57% (Figure 2d.)[2] with a 30Cp solution. However, if the injection force used is reduced with the BD Neopak™ XtraFlow™ 8mm UTW, the injection time may be similar, and the participant will feel the benefit in terms of injection force reduction as shown in **Figure 4** when looking at the reasons for preference for the BD Neopak™ XtraFlow™ 8mm UTW syringes tested.[5]

64% of patients preferred the BD Neopak™ XtraFlow™ 27G 8mm UTW syringe over the BD Neopak™ 27G 12.7mm STW syringe[5]

During the same Human Factor study patient participants were asked to give their preference and reasons for preference between the two syringes (BD Neopak™ XtraFlow™ 27G 8mm UTW and BD Neopak™ 27G 12.7mm STW) after having simulated subcutaneous self-injections.[5]

- BD Neopak™ XtraFlow™ syringe 8mm 27G UTW — 50; 64%
- BD Neopak™ syringe 12.7mm 27G STW — 11; 14%
- No preference — 17; 22%

Easier / Shorter Needle (word cloud: Less Scary, Thin, More Stable, Multiple Injections, Medicine Benefit, Easier Cap Removal, Less Comfortable, Hand Disabilities, Smoother, Smaller the better, Better Grip, Better Experience, Faster...)

Figure 4: Human Factors study probed for syringe preference amongst all users (N=39) with two solution viscosities (10cp and 30cp). 64% of self-injecting chronic disease patients (naive and experienced) preferred the BD Neopak™ XtraFlow™ (27G 8mm UTW) syringe for the reasons illustrated in the word cloud on the right.[5] The main reason (56% of the total reasons) given for this preference was the injection force reduction felt with the BD Neopak™ XtraFlow™ syringe, followed (at 34% of the total reasons given) by the shorter needle length.[5] The shorter needle (8mm instead of 12.7mm) was perceived by the participants as less anxiety-inducing and potentially less painful.[5] This correlates with the findings of Schwartz et al.[6] showing that shorter needles have a direct impact on injection-related anxiety and pain perception in patients using pens with exposed needles. In the 14% of participants who preferred the BD Neopak™ 12.7mm STW syringe, the longer needle length linked to more confidence about being at the right site, having control over the injection speed and having an easier injection. The cause for the 12.7mm STW syringe preference may be explained by fatiguability (for hand impaired participants) or confusion, if the participants applied a similar force on the plunger rod to deliver the solution. In that case, the injection time is reduced with the BD Neopak™ XtraFlow™ 8mm UTW syringe[2] but the participant may not notice that during its simulation.

Perspective – Figure 2 to 4

This **Human Factors study** shows the high variability in injection times (Figure 3) and probably injection forces used by patients when looking at manual self-injection with prefilled syringes.[4] This variability is inherent to Human nature as everyone possesses his/her own physical capabilities, experience, intuition, perception, fears, pain resistance, etc. that will impact their injection experience.

The theoretical injection force reduction with the 8mm UTW syringe shown in Figure 2 was positively felt by participants and was the first reason of preference compared to the 12.7mm STW syringe[5] (Figure 4). Interestingly, while the mathematical model also predicts up to 57% reduction of injection time[2] with the 8mm UTW syringe (Figure 2d.) this reduction in solution delivery time was not felt by most patients during injection simulation.[4,5]

Indeed, injection time was measured during the simulations comparing the two syringes and results show that patient participants performed the injections almost as quickly with the STW 12.7mm syringe as with the 8mm UTW syringe.[4] However, the global relative reduction in injection time measured with the 8mm UTW syringe indicates that patients probably used less force to inject with the 8mm UTW syringe but possibly not as low as predicted by the theoretical model.

This attempts to provide perspective on the preference data presented in Figure 4, where some patients did not feel any difference between the two tested syringes or when the reason for preference over the 8mm UTW syringe was its shorter needle length and not the injection force reduction. It is reasonable to assume that for some patients the injection force used was sensibly the same with both syringes and only the injection time varied. This variation in injection time may have went unnoticed or was not perceived by the end user as a strong differentiating factor leading to a syringe preference.

Note that these conclusions are related to manual self-injection and that they would probably be different if the syringes are integrated in auto-injectors. Indeed, holding time has been demonstrated to be an important factor in user experience when performing automatic subcutaneous injections.[7]

Reducing needle length from 12.7mm to 8mm can reduce intramuscular injection risk by 2.5 to 8 times in adults self-injecting without increasing intradermal injection risk[5]

Injecting into the right tissue is critical to ensure drug efficacy and avoiding clinical risks from other routes of administration. For the parenteral treatment of chronic conditions, subcutaneous injections are one of the preferred method of administration, especially when it comes to biologics.[8] A study assessing human skin layers thickness for various injection sites was conducted by Gibney et al. in 2010 on 388 adults.[9] Using an internal mathematical model, the risks of injecting into the wrong tissue (i.e. intramuscular or intradermal) when simulating subcutaneous injections without skin pinch with different needle lengths and two commonly used injection angles were calculated,[5] shown in **Figure 5b**.

Figure 5a: Schematic representation (not to scale) of human skin and subcutaneous layers. The thickness values mentioned on the figure represent 95% confidence intervals starting from Gibney et al. article[9] where those tissue thicknesses were measured on 388 adults (of various ages, genders, ethnicities and body mass index scores).

Legend: % risk of occurrence: <5%, 5-30%, 30-70%, >70%

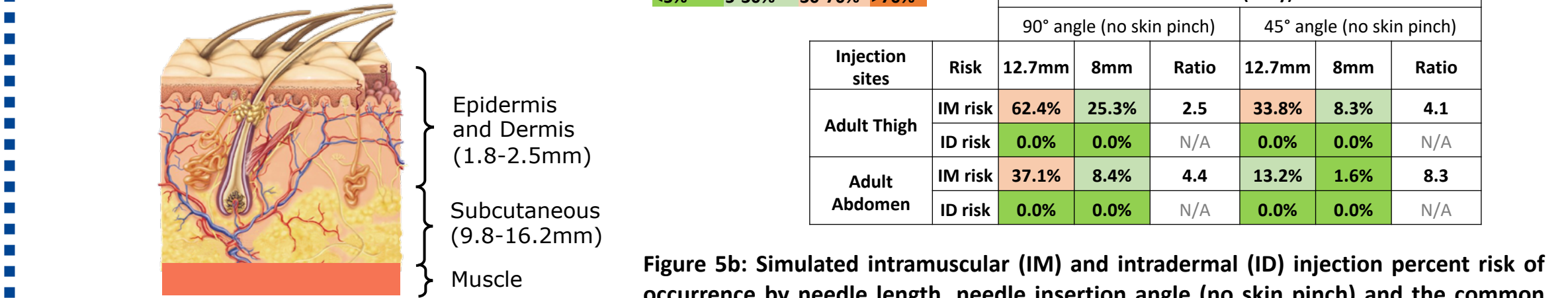| Injection sites	Risk	Adults (>18y)					
		90° angle (no skin pinch)			45° angle (no skin pinch)		
		12.7mm	8mm	Ratio	12.7mm	8mm	Ratio
Adult Thigh	IM risk	62.4%	25.3%	2.5	33.8%	8.3%	4.1
	ID risk	0.0%	0.0%	N/A	0.0%	0.0%	N/A
Adult Abdomen	IM risk	37.1%	8.4%	4.4	13.2%	1.6%	8.3
	ID risk	0.0%	0.0%	N/A	0.0%	0.0%	N/A

Figure 5b: Simulated intramuscular (IM) and intradermal (ID) injection percent risk of occurrence by needle length, needle insertion angle (no skin pinch) and the common self-injection sites of the abdomen and the thigh.[5] Simulations show that adopting a shorter 8mm needle could reduce the risk of intramuscular injection by 2 to 8 times without increasing the risk of intradermal injection for adult patients even if the recommended subcutaneous injection techniques[10] (i.e. 90° or 45° injection angles with skin pinch) are not performed or are done incorrectly.[5] This benefit can be particularly interesting for at-risk populations (i.e. Children and lean adults). Additionally, intradermal injections may lead to unwanted immune responses, especially with biologic drugs.[11] The Human Factors study showed that 38.5% of participants chose their abdomen to simulate subcutaneous self-injections and 61.5% chose the thigh.[5] Risks were calculated with an internal mathematical model based on adult skin layer thicknesses (n=388 adults of both genders, various ages, ethnicities and Body Mass Index scores)[9] and considering two commonly used injection angles.

Note: For children and lean adults (or those suffering from diseases that reduce subcutaneous tissue thickness), IM injection risk percentages are higher.[12] More generally, a skin pinch is recommended at 90 degrees before inserting the needle, for all patient populations in order to further minimize IM injection risk.

36% of simulated subcutaneous injections were performed with a non-recommended injection technique by naïve and experienced self-injecting chronic disease patients[5]

Injection technique data was generated from 39 patient participants suffering from chronic diseases[5] shown in Figure 6. Three user groups are represented: "Naïve" participants are those with chronic diseases without experience of self-injection or injection to others in the past 10 years; "Experienced" participants are those with chronic diseases and ongoing or recent PFS or syringe & vial treatment(s) with a minimum duration of 6 months that included at least 12 self-injections; "Experienced with hand impairment" participants are those participants who fit the "Experienced" criteria and have chronic diseases such as Rheumatoid Arthritis that affect hand use. Participants were asked to simulate subcutaneous self-injections using two different syringe configurations: BD Neopak™ XtraFlow™ 27G 8mm ultra-thin wall and BD Neopak™ 27G 12.7mm special thin wall.
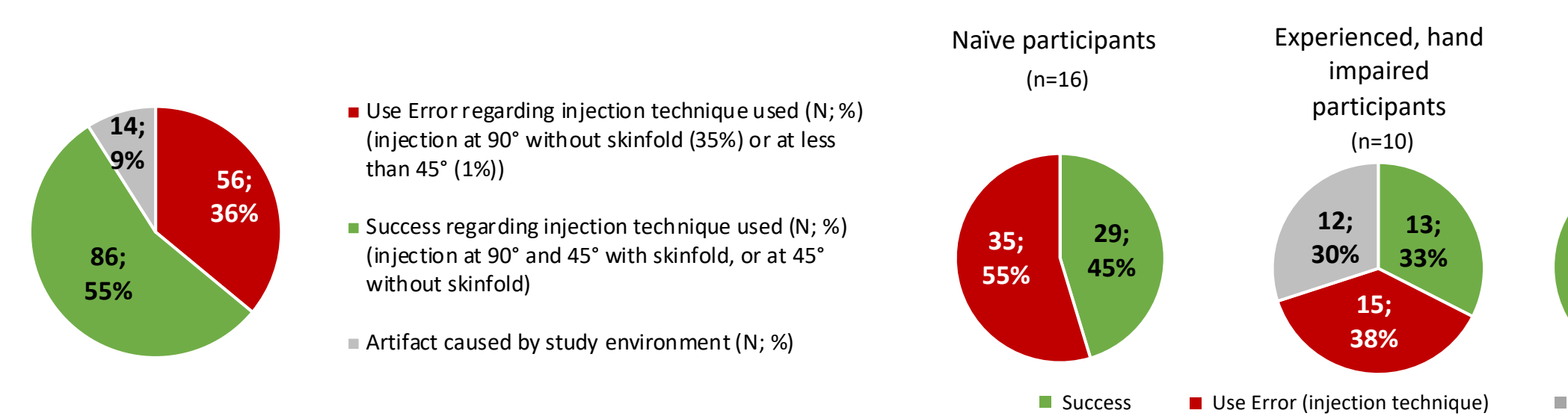

- Use Error regarding injection technique used (N; %) (injection at 90° without skinfold (35%) or at less than 45° (1%))
- Success regarding injection technique used (N; %) (injection at 90° and 45° with skinfold, or at 45° without skinfold)
- Artifact caused by study environment (N; %)

Naïve participants (n=16): 14; 9% / 56; 36% / 86; 55%
Experienced, hand impaired participants (n=10): 12; 30% / 13; 33% / 15; 38%
Experienced participants (n=13): 6; 12% / 2; 4% / 44; 85%

- Success
- Use Error (injection technique)
- Study artifact

Figure 6a: Usability results on injection technique for all subcutaneous injections simulated by participants (N=156 simulated injections) shows that the number and prevalence of simulations performed with a non-recommended injection technique was high and independent of the syringe configuration. 54 injections (or 35%) were performed at 90° without skin pinch and 2 injections (or 1%) had a needle insertion angle below 45°. These were coded as use errors. 14 injections (9%) performed at 90° and without skin pinch were classified as study artifacts, meaning that these were simulations wherein participants didn't perform their usual correct injection technique due to the study environment (i.e. bias mostly due to the foam pad).[5]

Figure 6b: Distribution of successes, use errors and study artifacts in injection technique among the different user groups (N=64 total simulations). Use errors linked to a non-recommended technique were observed in the majority for naive participants (55%). 38% of use errors was also observed in the group of experienced participants with a moderate hand impairment, 30% of whom engaged in incorrect injection techniques due to study environment. Those participants did not perform a correct injection technique (90° without skinfold), using a shorter 8mm needle instead of a 12.7mm would reduce the risk to injecting in the muscle by 2.5 to 8 times as shown in Figure 5.

Needle-related anxiety is reduced with short needles for both naïve and experienced self-injecting patients[5]

Short needles have a direct impact on injection-related anxiety and pain perception in patients using pens with exposed needles as shown in a study in the diabetes care space.[6] In a recent Human Factors study naïve patient participants were asked to rate their anxiety when faced with two syringe needle lengths for subcutaneous injection[5] presented in Figure 7.

Worst anxiety ever — 27G 12.7mm STW: 53% / 27G 8mm UTW: 34%

- Anxious — 13; 57%
- Not anxious — 10; 43%

(word cloud: Not Comfortable, Never Thinking, Medicine, Long Needle, Pain, Scary, Injection, Side Effects, Anxiety)

Figure 7a: Anxiety results (VAS scores) for naïve participants (N=16). Prior to any simulations, two uncapped syringes were presented to naïve participants to assess their anxiety level using a Visual Analog Scale (VAS). The results show that the BD Neopak™ XtraFlow™ syringe (27G 8mm UTW) was rated as less anxiety-inducing than a similar looking syringe with a 12.7mm 27G STW needle.[5] Note: such simulated Human Factors studies introduce a bias, as participants are aware that they will not actually inject themselves.
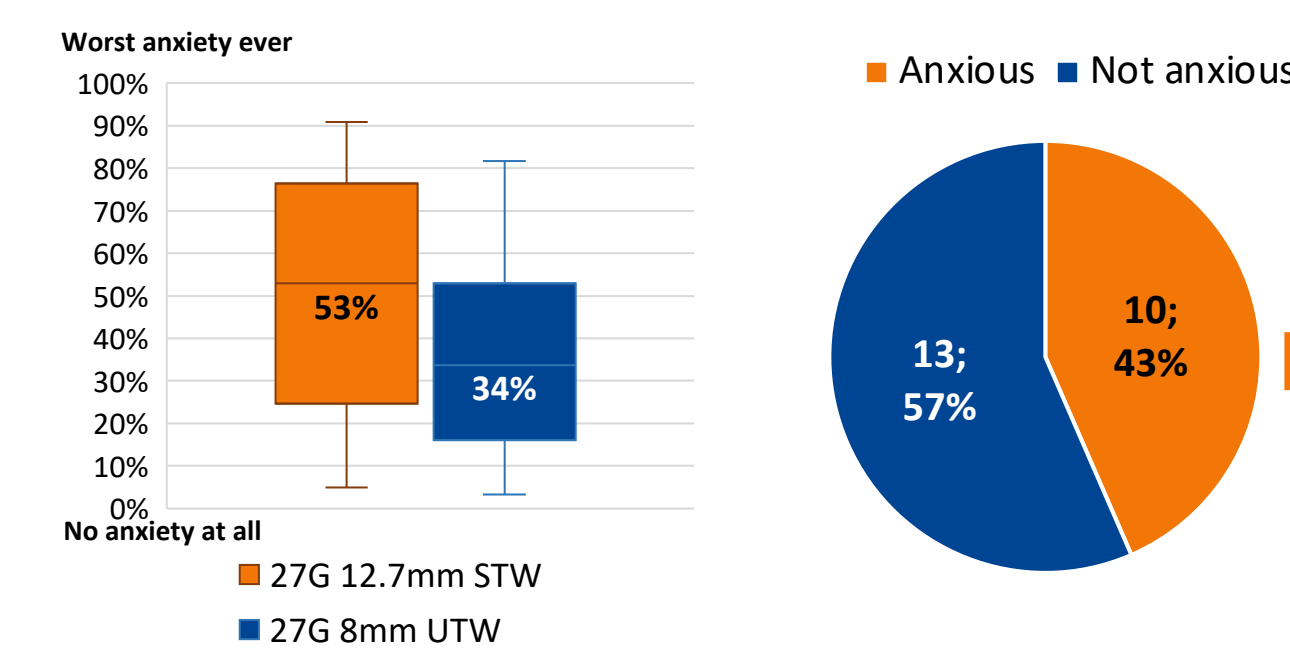
Figure 7b: Self-injection anxiety feedback in experienced participants (N=23). After the simulated injections, experienced participants were asked if they felt anxiety when self-injecting with PFS or syringes & vials.[5] even if the recommended injection technique[4] (45° with or without skin pinch, 90° with skin pinch) is not applied by allowing delivery of higher volume (up to 2mL) or higher viscosity drugs with substantial reduction in injection effort or time.[2,3] and by reducing patients' needle-related anxiety.[5]

Conclusions

Shorter 8mm needles combined with ultra-thin wall cannula technology (BD Neopak™ XtraFlow™*) bring benefits to subcutaneous chronic drug delivery and the patient injection experience in the following ways:

✓ Shorter 8mm needles with ultra-thin wall technology **reduce injection force** by up to 46% for 30cP solutions at a fixed injection time or reduce injection time by up to 57% for 30cP solutions at a fixed injection force (as shown by mathematical simulation of manual subcutaneous injection and R&D bench test).[2,3] Participants in the Human factor study performed the simulated injections more rapidly with the 8mm UTW needle syringes[4] and **positively felt the reduced injection force** allowed by the XtraFlow™ syringe[5] as cites in the patient preference results.

✓ 8mm needle length at a 90° or 45° angle with no skin pinch for abdomen and thigh injection sites **reduces IM injection risk by 2.5 to 8 times in adults.**[4] The Human Factors study showed a **high proportion (35%) of such non-recommended subcutaneous injection technique**, even in experienced self-injecting patients.[5]

✓ **Needle-related anxiety is reduced with shorter needles** for both naive and experienced self-injecting patients.[5] The Human Factors study showed that 43% of experienced patients (including highly experienced patients) are still anxious when self-injecting and that 96% of experienced patients see advantages to the short 8mm needle.[5]

BD Medical – Pharmaceutical Systems is launching the BD Neopak™ XtraFlow™ syringe* both in 1mlL and 2.25mL (see Image 1) formats. BD Neopak™ XtraFlow™ is designed to improve subcutaneous drug delivery accuracy and patient injection experience for chronic therapies in three ways: by improving reliability of injecting into target tissue[5] even if the recommended injection technique[10] (45° with or without skin pinch, 90° with skin pinch) is not applied by allowing delivery of higher volume (up to 2mL) or higher viscosity drugs with substantial reduction in injection effort or time[2,3] and by reducing patients' needle-related anxiety.[5]

Integrated system solutions with BD Neopak™ XtraFlow™ syringes: Complementing its large portfolio of delivery solutions for chronic injectable drugs, BDM-PS will soon integrate BD Neopak™ XtraFlow™ syringes with BD UltraSafe Plus™ safety devices* for the prevention of needlestick injuries. BD Neopak™ XtraFlow™ syringes will also be integrated into self-injection devices, including the BD Intevia™ 2.25 mL autoinjector*.

Image 1: BD Neopak™ XtraFlow™ 2.25 mL Glass Prefillable Syringe Platform with 12.7mm STW and XtraFlow™ 8mm UTW needle solutions, addressing the needs of viscous/high volume biologics.

> **The feedback reported here through the Human Factors study reminds us that self-injecting medication is not an easy task for patients, even if they are experienced at injecting themselves. Thus, improving the injection experience should be considered a priority, especially in chronic space where patients must inject themselves frequently and often over an extended period.**

References

1. Prefilled Syringe Customer Requirements Research, Voice of the Customer [internal study], Le Pont-de-Claix, France; Becton, Dickinson and Company, 2018 ; 2. Injection time and ejection force calculation [internal study], Le Pont-de-Claix, France; Becton, Dickinson and Company, 2020 ; 3. BD Neopak™ XtraFlow™ 2.25 mL portotype evaluation [internal study], Le Pont-de-Claix, France; Becton, Dickinson, 2020 ; 4. "Human Factors Formative Study – Usability and Acceptance of a New Syringe Compared to Standard for 2.25 mL BD Neopak™ Syringe," [internal study], BD, 2019. 5. Pager et al. (2020), "User experience for manual injection of 2 mL viscous solutions is enhanced by a new prefillable syringe with staked 8mm ultra-thin wall needle", Expert Opinion on Drug Delivery, https://doi.org/10.1080/17425247.2020.1796630 ; 6. Schwartz, S., et al. (2004), "A multicenter, open-label, randomized, two-period crossover trial comparing glycemic control, safety, and preferences achieved with a 31 gauge x 6 mm needle versus a 29 gauge x 12.7 mm needle in patients with diabetes mellitus", Clin Ther., Vol 26 (10), p. 1663-1678 ; 7. Guerlain et al. "A comparison of 4 epinephrine autoinjector delivery systems usability and patient preference", Elsevier, 2010, Vol104(2), pp172-177 ; 8. Viola M, Sequeira J, Seica R, et al. « Subcutaneous delivery of monoclonal antibodies: how do we get there?", J Control Release. 2018;286:301–314 ; 9. Gibney, M.A., et al. (2010), "Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations", Curr Med Res Opin, Vol. 26 (6), p. 1519-30 ; 10. "Principles of Injection Technique". Company Publication, BD, 2017 ; 11. Baker, M.P., et al. (2010), "Immunogenicity of protein therapeutics: The key causes, consequences and challenges", Self Nonself, Vol. 1 (4), p. 314–322 ; 12. Le Presti, D., C. Ingegnosi and K. Strauss (2012), "Skin and subcutaneous thickness at injecting sites in children with diabetes: ultrasound findings and recommendations for giving injection", Pediatr Diabetes, Vol. 13 (7), p. 525-533.
*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.