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Analysis and Perspective of Dosing Accuracy and Insulin Flow Rate Characteristics of a New Disposable Insulin Pen, FlexTouch, Compared with SoloSTAR

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Abstract

Pen injectors for the administration of insulin have been available since the 1980s. The first insulin pen, NovoPen®, was introduced by Novo in 1985 (*http://www.novonordisk.com/about_us/history/step-by-step.asp*). In the years since, insulin pens have seen innovation in both features and functionality, and many more manufacturers have entered the market. This analysis discusses several features and design alternatives of insulin pens and comments on a new study by Bohnet and coauthors in this issue of *Journal of Diabetes Science and Technology* that compared the dosing accuracy of the spring-driven FlexTouch® (FT; Novo Nordisk; insulin aspart) with that of the manually operated SoloSTAR® (Sanofi; insulin glulisine). The volumetric flow rate of insulin delivery with FT was also evaluated.

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The first international standards (ISO 11608 family) governing pen-injector design verification were published in 2000 and established a series of general design requirements for the user interface as well as dose accuracy limits and important mechanical and environmental challenges targeting product robustness.[1] To avoid unnecessarily restricting innovation, the standards were careful not to be overly design prescriptive. 2012 versions of the ISO 11608 family (including a new part addressing automated functions) have been published.[2] The scope was expanded to include all needle-based injection systems and syringes. All aspects of safety and robustness were expanded, including a heightened focus on human factors testing and risk analysis.

For the purpose of this review, general product robustness was assumed and needle attributes (length, gauge, sharpness, and siliconization) as a function of accuracy and insertion pain were ignored. It is assumed that patients will choose an appropriate needle based on preference and availability.

The article by Bohnet and coauthors[3] in this issue of *Journal of Diabetes Science and Technology* demonstrates that both pens meet the International Organization for Standardization (ISO) requirements for dose accuracy. However, it remains to be demonstrated whether the statistically significant difference noted in favor of SoloSTAR® (SS; Sanofi;

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Abbreviations: (FT) FlexTouch, (ID) inner diameter, (ISO) International Organization for Standardization, (SS) SoloSTAR

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insulin glulisine) at the high dose is clinically significant. While the article discusses ISO compliance with individual doses, the standard only mandates that the accuracy distribution fall within those limits. While outliers would certainly increase variability and the likelihood of failure, it should be noted that the ISO 11608-1 makes no such requirement. Furthermore, it remains unclear why study results demonstrating no individual doses were outside the specification limits disproves former studies demonstrating the converse. Given numerous sources of variability (e.g., lot-to-lot and interpen variability) in conducting such studies, the current and former studies remain equally valid.

With regard to the assumptions made relative to flow rate and injection site discomfort, a broader perspective may be helpful. Firstly, it is not clear that rates reported in this study (i.e., peak mean flow rate of 15.61 U/s) have a negative impact on comfort, particularly given the rapid growth of autoinjectors operating with larger volumes and higher injection rates. Another important aspect of injection comfort is the overall dwell time of the needle in the injection site, which consists of completing the injection stroke as well as waiting the recommended time for the system to relax (e.g., air bubbles, elastomeric components) before removing the needle from the skin. With longer dwell times comes greater opportunity for instability or needle movement and, therefore, greater likelihood of discomfort. Given the well-characterized higher injection speeds (80.52% of injection stoke at speeds greater than 10 U/s for FlexTouch® [FT; Novo Nordisk, insulin aspart] compared with a typical testing speed of 6 to 10 U/s for the SS)[4] in conjunction with a shorter hold time (6 s for the FT and 10 s for the SS), overall dwell time for the FT would be considerably shorter than for the SS. Secondly, the ergonomics of dose actuation should be considered. At 80 U, the SS requires a thumb reach of approximately 3.43 cm. For smaller hands or those with dexterity issues, it may be difficult to properly position one's thumb and initiate dosing without creating higher injection forces. This may create additional needle instability. Finally, while both designs allow the user to interrupt an injection midstroke, the SS does have the added advantage of allowing the user to alter injection speeds (e.g., to reduce injection force).

Given the diversity of individuals with diabetes, it is understood that various feature sets serve different demographics and patient needs. No one design is necessarily superior to another if it meets the requirements of the ISO 11608 series. The German Diabetes Association recommendations noted make sense for thumb-actuated devices like the SS (i.e., slowly and smoothly), particularly given the 3.43 cm stroke length. However, that recommendation may have no relevance to a spring-driven device such as the FT where contributions to injection force [e.g., needle inner diameter (ID), internal part friction, and ergonomics] are isolated from the user through a spring-driven delivery mechanism.

Accuracy and pain minimization are paramount. However, from the broader safety perspective, patient confidence in the device and how it functions are also important. Lack of confidence may lead to use errors when, for example, a patient doubts delivery of the full dose and takes a second dose. Patients may prefer to participate in their injection whereby depressing the dose knob themselves provides certainty. To that end, the SS may offer that confidence compared with the "automated delivery" of the FT. To further explore design tradeoffs, the length of the SS when fully dialed out to the 80 U setting is just over 17.78 cm compared with the FT at 13.97 cm. Here, given the considerable size difference, the FT may offer a modicum of discretion when used in public. Both pens prevent the user from dialing doses greater than the remaining volume and both offer dialing and injection clicks. They also offer a return to "0" dose confirmation. The FT also has an end-of-dose click with the added benefit of confirming dose delivery by nonvisual means.

With regard to the FT flow rate measurements, it should be noted that the ID of the needle, which was not specified in their article, would have a material impact on flow rate and injection time measurements. The outer diameter, typically expressed in terms of gauge (i.e., 32 G, as mentioned in the paper) is not a good indicator of ID, because wall thickness varies. One would, therefore, expect FT injection time and flow rate to vary with needle selection and the spring specifications. With regard to the SS, needle ID will impact injection forces and, therefore, stability of the needle in the injection site. The user can compensate for smaller ID and increased injection forces by pushing the SS dose knob more slowly.

The FT flow rate curve depicted in Figure 2 of the article by Bohnet and coauthors[3] and the observation of higher dialing torque as the dose size increases is to be expected for spring-driven pens. The reality of such a design likely explains the bigger diameter of the FT (i.e., increased torque arm), as this assists the user in dialing larger doses.

In conclusion, both products appear to satisfy the general design and accuracy requirements defined by ISO 11608-1. Given the focus on higher doses, a modest advantage is ascribed to the FT in terms of discretion and ease of use at higher doses. The SS allows the user to participate in the injection. Nevertheless, they both represent reasonable alternatives for patients deciding how best to administer their insulin. While the article highlights a number of assumed differences between the two devices in terms of accuracy and comfort, further clinical or human factors studies would be required to determine whether these differences are clinically meaningful. As such, no benefit of one pen over the other should be ascribed in terms of accuracy or comfort when evaluating the increased volumetric flow rate with the FlexTouch compared with standard mechanical pen injectors such as the SoloSTAR.

Disclosures:

Both authors are employees/shareholders of Eli Lilly and Company. Debra Ignaut is a U.S. expert on the ISO Technical Committee 84. Harold Yeager is the chairman of the ISO Technical Committee 84. The 11608 Family of Standards is published under Technical Committee 84.

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