

# Dosing Accuracy of Two Disposable Insulin Pens According to New ISO 11608-1: 2012 Requirements

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## Abstract

**Objective:** The aim was to compare 2 disposable insulin pens, FlexTouch® (Novo Nordisk, insulin aspart) and SoloSTAR® (Sanofi, insulin glulisine), according to new ISO 11608-1:2012 requirements for dosing accuracy.

**Methods:** Sixty pens of each type were tested at 1, 40, and 80 U doses. Following the new ISO requirements, each dose was delivered from the front, middle, and rear one-third of the pen. Statistical analysis was performed using Student's *t* test.

**Results:** Both pens delivered all doses within ISO limits. The difference between the average measured dose and the target dose was significantly smaller for SoloSTAR than FlexTouch at 40 U ( $P = .009$ ) and 80 U ( $P = .008$ ), but not at 1 U ( $P = .417$ ).

**Conclusion:** Both insulin pens fulfilled the dosing accuracy requirements defined by ISO 11608-1:2012 at all 3 dosage levels.

## Keywords

disposable insulin pens, dosing accuracy, FlexTouch, SoloSTAR

Patients with diabetes generally prefer insulin pens over vial and syringe because of the ease of use, discreetness of injection, and portability of the pens.<sup>1-3</sup> Insulin pens account for over 60% of insulin delivery worldwide.<sup>4</sup> Conversion from vial and syringe delivery to insulin pens is associated with improved medication adherence and reduced likelihood of hypoglycemic events, due in part to the greater dosing accuracy of pens.<sup>4-6</sup>

To assure the accuracy of the injected dose, insulin pens need to fulfill ISO 11608-1 requirements for dosing accuracy, which they have demonstrated in several studies.<sup>4,7-11</sup> Substantial modifications have been made to the ISO requirements for needle-based injection systems; the new requirements differ from the old in defining the design of dose delivery, with each tested dose delivered from the front, middle, and rear one-third of the pen cartridge.<sup>12</sup>

Recently, FlexTouch® (FT), a disposable insulin pen with a spring-loaded mechanism, has been introduced as another pen option. The aim of the present study was to compare the dosing accuracy of SoloSTAR® (SS) with FT according to the new ISO 11608-1:2012 requirements.<sup>12</sup> The 2 pens were previously compared according to the ISO 11608-1:2000<sup>13</sup> requirements at which both showed excellent dosing accuracy.<sup>7,14</sup>

## Methods

SS pens (sanofi-aventis Deutschland GbmH, Frankfurt, Germany) were purchased from a German pharmacy, while FT pens (Novo Nordisk A/S, Bagsvaerd, Denmark) were obtained through an international pharmacy in the United Kingdom. The pens were shipped under cool conditions (36–46°F) and stored both unopened and while in use as indicated in the Information for Users for each pen type. An overview of the tested pens and corresponding injection needles is listed in Table 1. Needles were applied according to the manufacturers' instruction leaflet.

Dosing accuracy was determined as described previously by Bohnet et al,<sup>7</sup> except that the dosing scheme

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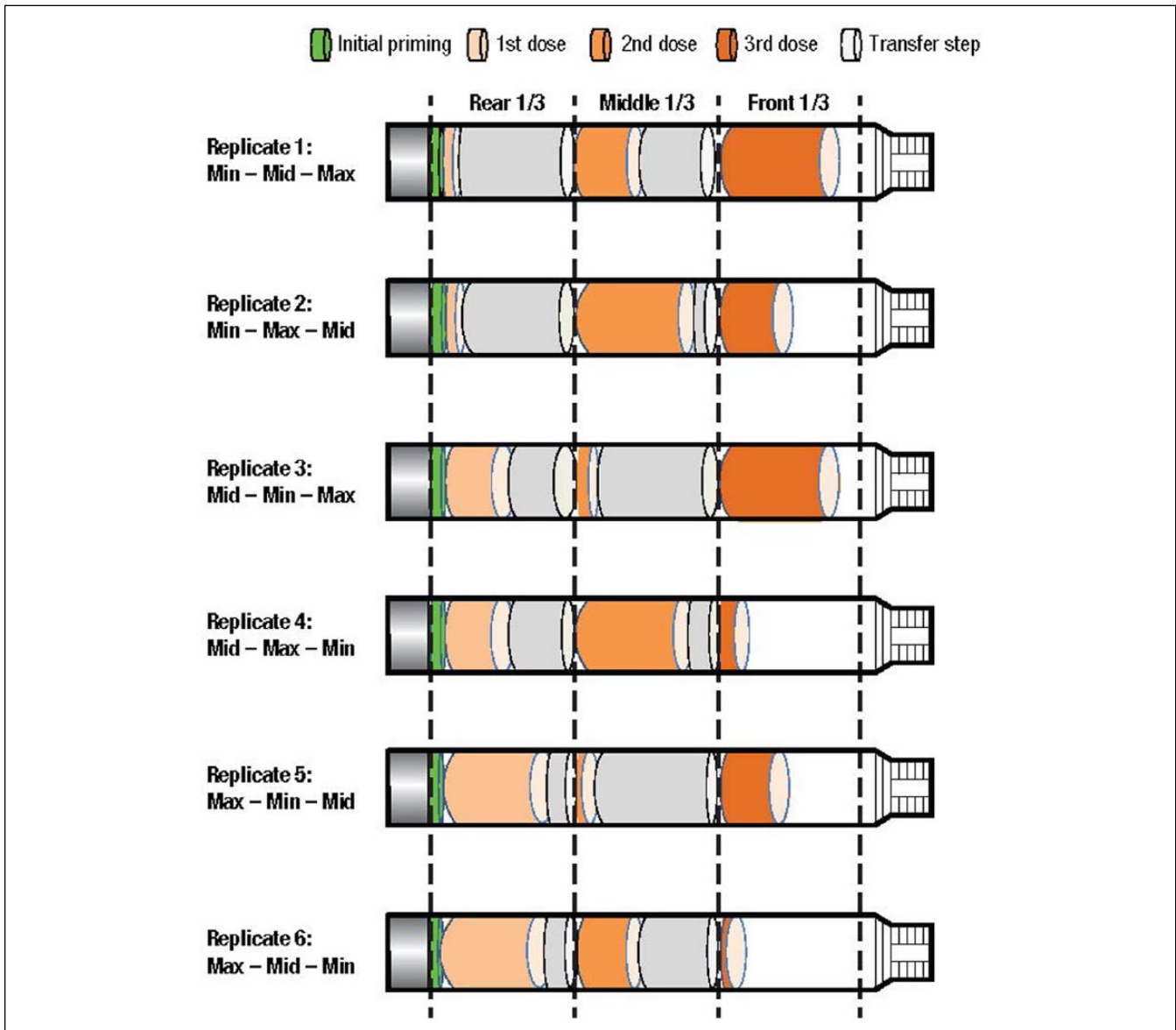
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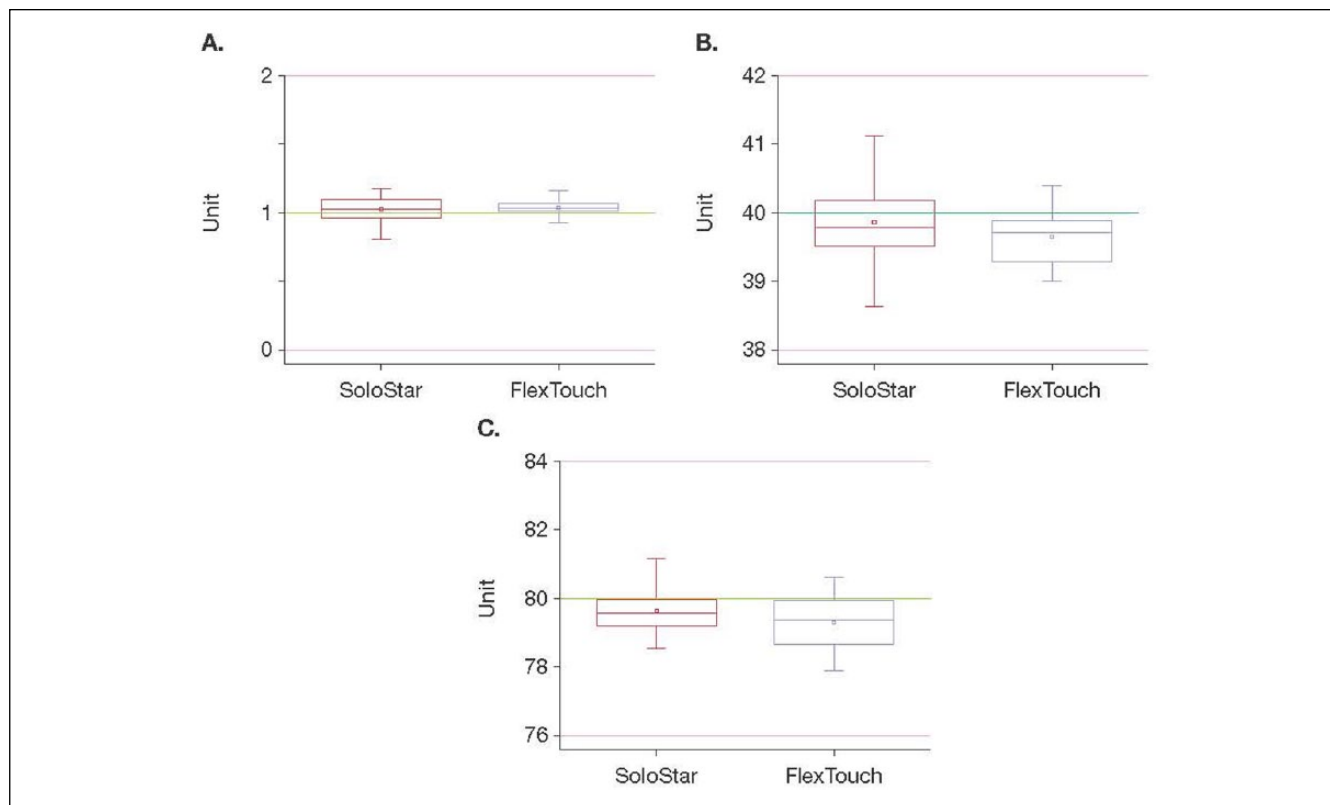
**Table 1.** Insulin Pens and Corresponding Needles Included in This Study.

Insulin pen	Manufacturer	Batch	Insulin	Needles
SoloSTAR	Sanofi	2F082A	Glulisine (Apidra®)	BD Micro-Fine (0.25 mm [31G] × 5 mm)
FlexTouch	Novo Nordisk	AP51446	Aspart (NovoRapid®)	NovoFine (0.25 mm [31G] × 6 mm)

**Figure 1.** Dosing scheme according to new ISO 11608-1:2012.

comprised 1 single measurement of each target dose per pen according to ISO 11608-1:2012 requirements.<sup>12</sup> Consequently, instead of 30 pens as per the former ISO standard,<sup>13</sup> 60 pens of each pen type were investigated. Furthermore, each target dose was delivered from the front one-third, middle one-third, and rear one-third of the pen cartridge with a corresponding transfer step in between the doses (Figure 1).

Target doses of 1 U (minimum), 40 U (middle), and 80 U (maximum) were ejected and measured for each pen. All measurements were performed by a single investigator to eliminate potential investigator variability. The individual insulin pens were operated according to each manufacturer's instruction leaflet. The plunger was kept depressed after each dose for 10 seconds and 6 seconds for SS and FT, respectively, to ensure that the entire dialed dose had been expelled.



**Figure 2.** Distribution of the actual doses of SoloSTAR and FlexTouch at the 1 U (A), 40 U (B), and 80 U (C) dosage levels. The line near the middle of each box represents the median (50th percentile). The lower and upper ends of the box represent the 25th and 75th percentiles. The small square is the mean. The ends of the whiskers represent the minimum and maximum values, respectively. The horizontal lines at 0 and 2 in panel A, 38 and 42 in panel B, and 76 and 84 in panel C represent the ISO limits for the 1U, 40U, and 80U dosage levels. The dose tested and the corresponding ISO limits are represented by the horizontal lines in each plot.

Each dose was deposited in a beaker containing a 0.5-1 cm layer of liquid paraffin. The dose was weighed immediately using an analytical balance (XP205/M, Mettler Toledo AG, Gießen, Germany) with an accuracy of 0.00001 g. The balance was zeroed before each dose of insulin was deposited and weighed. Weights were corrected for the relative density of each insulin formulation (1.0066 for insulin aspart; 1.0072 for insulin glulisine). For each dose application, a new injection needle was used and an air shot included before the injection.

The arithmetic average of the actual doses was calculated, as well as the standard deviation, the average deviation (percentage) from the target dose, and the statistical tolerance interval. The evaluation of dose accuracy was based on the guidelines of the ISO 11608-1:2012,<sup>12</sup> allowing a deviation not more than  $\pm 1$  U at the 1 U (0-2 U) dosage level,  $\pm 5\%$  ( $\pm 2$  U) at the 40 U (38-42 U) dosage level, and  $\pm 5\%$  ( $\pm 4$  U) at the 80 U (76-84 U) dosage level. In addition, the calculated statistical tolerance interval for each pen should lay within the specified upper and lower acceptance limits for each target dose by using a 95% confidence interval and probability content of  $P = .975$  for 60 measurements.<sup>12</sup> To compare the dose accuracy of SS and FT, statistical analysis was

performed using Student's *t* test. A *P* value  $< .05$  was considered to be statistically significant.

## Results

Both insulin pens showed excellent dosing accuracy at all dosage levels (Figure 2). The average values of the actual measured doses were closer to the target dose for SS at all 3 dosage levels compared with FT (Table 2). Differences between average values of the actual dose from the target dose were statistically significant at the middle 40 U dose (SS:  $-0.12$ ; FT:  $-0.34$ ;  $P = .009$ ) and the maximum 80 U dose (SS:  $-0.36$ ; FT:  $-0.67$ ;  $P = .008$ ) in favor of SS; the difference was not significant at the minimum 1 U dose (SS:  $+0.03$ ; FT:  $+0.04$ ;  $P = .417$ ). The average relative deviation of the actual dose from the target dose was  $+2.69\%$  and  $+3.91\%$  at the minimum,  $-0.31\%$  and  $-0.85\%$  at the middle, and  $-0.45\%$  and  $-0.84\%$  at the maximum dose for SS and FT, respectively. No single dose of SS or FT was detected outside the specified limits, and the statistical tolerance intervals defined by the ISO standards were met by both pens at all 3 dosage levels (Table 2).

**Table 2.** Overview of the Average Actual Doses, Standard Deviation, and Statistical Tolerance Interval at Each Dosage Level for SoloSTAR and FlexTouch.

Pen	Target dose (U)	Actual dose		
		Average dose (U)	Standard deviation (U)	Statistical tolerance interval (U) <sup>a</sup>
SoloSTAR	1	1.03	0.10	0.77-1.28
FlexTouch	1	1.04	0.05	0.90-1.17
SoloSTAR	40	39.88	0.50	38.53-41.22
FlexTouch	40	39.66	0.36	38.69-40.63
SoloSTAR	80	79.64	0.60	78.04-81.24
FlexTouch	80	79.33	0.70	77.46-81.19

<sup>a</sup>According to the International Organization for Standardization (DIN EN ISO 11608-1:2012), the acceptance range for the statistical tolerance interval is 0-2 U for the 1 U dosage level, 38-42 U for the 40 U dosage level, and 76-84 U for the 80 U dosage level.

## Discussion

The present study demonstrates that both SS and FT meet the new ISO 11608-1:2012<sup>12</sup> requirements for dosing accuracy at ambient temperature. Applying the new dosing scheme with single measurements of each target dose delivered from the front, middle, and the rear one-third of the pen and the higher sample size of 60 pens for each pen type, the average deviation between actual and target dose and the standard deviation remained very low for both pens.

In addition to the significantly better dosing accuracy at maximum dose (80 U) with SS reported by Bohnet et al<sup>7</sup> when applying ISO 11608-1:2000,<sup>13</sup> the current study revealed significantly closer actual doses with SS at 40 U and 80 U compared with FT. However, the difference in dosing accuracy between SS and FT cannot be considered clinically relevant.

Wielandt et al<sup>14</sup> reported significantly better dosing accuracy for FT than SS at 1 U. This could not be confirmed according to the new standard in the current study where equivalent results were obtained with the 2 pens. Götzche et al<sup>15</sup> also reported equivalent dosing accuracy according to the new ISO requirement at 1 U, 40 U, and 80 U for SS and FT. However, contrary to the new ISO 11608-1:2012<sup>12</sup> requirement, only 30 insulin pens with a dosing scheme comprising 2 single measurements of each target dose per pen were used. In the current study, all single doses, 180 with each pen, were delivered within the ISO limits, despite the larger pen sample size.

The current results confirm the excellent dosing accuracy for SS<sup>4,7-11</sup> and FT<sup>7,14</sup> demonstrated in previous studies performed according to ISO 11608-1:2000.<sup>13</sup> Furthermore, the results demonstrate that the spring-loaded mechanism of FT, which is less dependent on the operator than SS, does not translate into a dosing accuracy advantage compared with the manually operated SS.

## Abbreviations

FT, FlexTouch; SS, SoloSTAR.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MS and SK are employees of sanofi-aventis Deutschland GmbH. MAT and MSZ have nothing to disclose.

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