# Prefilled insulin device with reduced injection force: patient perception and accuracy

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ABSTRACT

Objective: The injection force and the patient perception of the Next Generation FlexPen* (NGFP) with design modifications aimed at reducing injection force was assessed. The accuracy and precision of the NGFP was also tested under standard conditions.

Research design and methods: Dosing accuracy was tested (according to ISO 11608 requirements) at 1 IU, 30 IU and 60 IU doses (acceptable limits were $1 \pm 1$ IU (0–2 IU), $30 \pm 1.5$ IU (28.5–31.5 IU), and $60 \pm 3$ IU (57–63 IU)). Pens were tested at reference conditions (18–28°C and relative humidity 25–75%). Delivered doses were measured on a sensitive balance and corrected for the specific density of the insulin aspart used (according to ISO 11608-1). Precision was calculated from the variance around the mean delivered dose. The injection force of NGFP was measured, and user-preference of NGFP and FlexPen (FP) were compared in 50 patients with type 2 diabetes.

Results: The mean injection force with NGFP and FP was $12.57 \pm 1.81$ N and $17.90 \pm 1.51$ N ($p < 0.001$), respectively. Almost twice as many patients rated the injection force as 'good' or 'very good' with NGFP (80%, 72% and 38% when delivering 20 IU, 40 IU and 60 IU, respectively) compared with FP (48%, 32% and 20% when delivering 20 IU, 40 IU and 60 IU, respectively) and 76% of patients rated NGFP as superior, in terms of simplicity and comfort, to FP. NGFP accurately delivered the set doses (means [SD] were 0.98 [0.06] IU, 29.98 [0.18] IU, and 59.93 [0.24] IU for the 1 IU, 30 IU and 60 IU doses, respectively).

Conclusions: These results show that NGFP has a 30% reduction in injection force compared with FP and was rated as 'more simple and comfortable to use' by patients. Furthermore, NGFP was as accurate and as precise as FP.

## Introduction

The use of insulin injections for the management of diabetes can be perceived as inconvenient and traumatic by patients. Many patients fear injections, find traditional vial and syringes inconvenient, and lack confidence in delivering accurate doses of insulin; these factors limit patients' overall confidence to self-manage their diabetes with insulin[1,2].

Partly because of injection fears and partly because the use of vial and syringe can lead to inaccurate dosing[3,4], injection pens are now the predominant devices for insulin delivery, especially in Europe. Pens overcome the patient's fear of injection, are convenient to use and increase confidence in dose delivery, and therefore, potentially improve the quality of life of the user[5–10]. Because it can have consequences for glycaemic control, the improved accuracy and precision of

*FlexPen is a registered trade name of Novo Nordisk A/S, Bagsværd, Denmark

tered[11,12], but the impact this may have on the frequency of hypoglycaemia or even more serious long-term consequences of poor glycaemic control has not been demonstrated.

FlexPen* (FP) is a prefilled insulin pen that is used by more than 3 million people with diabetes[14]. The dosing accuracy and consistency of FP has been confirmed in several studies[15–18]. It is known that some insulin pens can, on rare occasions, block if the push button is pushed at an oblique angle, and the manufacturer has received occasional reports that patients found the push-button hard to push down. To overcome these issues and to reduce the injection force, a Next Generation FP (NGFP) has been designed. The NGFP has changes to the ratchet, the clutch and the push-button to reduce the injection force and to eliminate blocking with FP. The other features of NGFP are exactly the same as FP. As with any new insulin pen, existing pens that undergo design changes must be shown to deliver accurate and reliable insulin doses during rigorous testing. Here we report on the dosing accuracy of NGFP compared with FP. The injection force of NGFP and FP was also tested in our study. In addition, we present the results of a questionnaire survey of user preference between NGFP and FP.

## Methods

All dose accuracy test methods were conducted in an identical manner with both NGFP and FP.

### Materials

The NGFPs tested for injection force and performance were all drawn from the same batch (lot TG 70313/A) and were filled with NovoRapid† (insulin aspart) (batch TZ60322). For the tests on FP, pens were drawn from batch SP50497 and filled with NovoRapid (insulin aspart) (batch RQ50794). Pens were picked randomly from these lots to perform each test. The same batches of pens were used for the user preference study.

### Calculation of dose accuracy

Accuracy was measured in the Novo Nordisk A/S Quality Assurance laboratory, all testers were suitably

All doses were delivered in a random order. The accuracy of dosing was measured by delivering 1 IU, 30 IU or 60 IU 60 times (180 doses in all) with each pen (according to ISO 11608-1). Each test was carried out with a new and unused pen, and before delivering each dose the pen was prepared according to ISO 11608-1 instructions. Doses were delivered onto a precision balance and weighed. Weights were corrected for the specific density of insulin aspart (1.008 g/ml at 5°C, 1.005 g/ml at 20°C and 0.999 g/ml at 40°C). Dose accuracy was measured at reference conditions: pens were exposed to 18–28°C and relative humidity (RH) 25–75% for at least 4 hours before measuring dose accuracy.

Acceptable limits for dose accuracy were based on ISO regulations (ISO 11608-1): $1 \pm 1$ IU (0–2 IU), $30 \pm 1.5$ IU (28.5–31.5 IU), and $60 \pm 3$ IU (57–63 IU). The mean value and standard deviations of the 60 doses delivered at each of the three settings (1 IU, 30 IU and 60 IU) were calculated. In addition, minimum, maximum and inter-quartile range values were recorded.

The difference between mean absolute deviation in the delivered dose of each pen was calculated using Stigma Stat v3.5. and the Levenes test was used to test for homogeneity of variance as a measure of pen precision.

### Injection force measurements

Injection force was measured under standard conditions with 20 previously unused pens with the cartridge and NovoFine‡ 30G 8 mm needle attached and at a flow rate of 10 IU/s.

### User preference questionnaire

In this part of the study NGFP and FP were compared for injection force perception by users. The survey recruited 50 patients with type 2 diabetes. The study was handled in accordance with local legal and ethical requirements and each patient signed an informed consent form before taking part in the study. All participants were receiving insulin at the time and used an insulin pen at least once per day. Test injections with insulin aspart (NovoRapid) were made into an injection pillow. Pens were fitted with 30G 8 mm needles, and each patient used a previously unused pen of each type.

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respectively (see Appendix). After delivering all doses and answering Questions 1–3, each patient answered Question 4 on pen 'simplicity and comfort' of use.

For the answers to Questions 1–3, data were modelled by logistic regression for ordinal response with pen and patient as fixed effects. A likelihood-ratio Chi-square test was used to test if pen type had a significant effect on answers. The responses to Question 4 were tested for equal 'simplicity and comfort' using a two-sided chi-square test. JMP version 7.0.1 was used for these analyses.

# Results

## Dose accuracy

Dose accuracy was well within the acceptable limits for NGFP and FP (Table 1). No single dose delivered by any pen (at 1 IU, 30 IU or 60 IU) was below or above the pre-specified acceptable ranges. The mean absolute deviation from the set doses for FP were 0.06 IU (6%), 0.23 IU (0.8%) and 0.36 IU (0.6%) for 1 IU, 30 IU and 60 IU, respectively. The corresponding values for NGFP were 0.05 IU (5%), 0.14 IU (0.5%; $p < 0.05$ compared with FP) and 0.19 IU (0.3%; $p < 0.01$ compared with FP) for 1 IU, 30 IU and 60 IU, respectively. The analysis of precision also showed that NGFP was significantly more precise when delivering doses of 30 IU ($p < 0.05$) and 60 IU ($p < 0.05$) than FP. Stress tests of NGFP at different temperatures and humidity (conducted according to ISO methodology) showed that there was no significant change in the dose accuracy under various environmental conditions (results not shown).

## Injection force

The mean injection force with NGFP was 12.57 N and this is considerably lower than the injection force with

The range of injection force measured with FP was 15.35–19.99 N, so all FPs had injection force higher than the mean injection force with NGFP.

## User preference survey

After delivering three doses with each pen, more patients rated the injection force with NGFP as 'good' or 'very good' than with FP (Figure 1). The difference in responses after using each pen was significant ($p < 0.0001$) for all three doses. An injection force rating of 'very good' or 'good' was given to NGFP by 80% of patients when delivering 20 IU, 72% when delivering 40 IU and 38% when delivering 60 IU – the corresponding proportions for FP were 48, 32 and 20%, respectively.

In response to Question 4, 76% of the patients stated that NGFP was 'simpler and more comfortable' to use than FP, and only 24% stated that FP was 'simpler and more comfortable' to use than NGFP. The hypothesis of equal 'simplicity and comfort' is rejected and shows that a significantly greater proportion of patients found NGFP more 'simple and comfortable' to use ($p = 0.0002$).

# Discussion

This study demonstrated that NGFP delivers insulin in an accurate and precise manner and is more 'simple and comfortable' to use than FP. The design modifications to NGFP have not adversely affected any of the previously demonstrated attributes of FP[15–18] but have reduced the injection force by 30% compared with FP. NGFP delivered doses were more accurate and precise (significantly for 1 IU) than FP delivered doses.

**Table 1.** *Accuracy and precision of NGFP and FP under standard conditions**

| Value | Dose of insulin delivered with NGFP | | | Dose of insulin delivered with FP | | |
| --- | --- | --- | --- | --- | --- | --- |
| | Set to 1 IU | Set to 30 IU | Set to 60 IU | Set to 1 IU | Set to 30 IU | Set to 60 IU |
| Mean | 0.98 | 29.98 | 59.93 | 1.04 | 29.93 | 59.90 |
| Standard deviation | 0.06 | 0.18 | 0.24 | 0.06 | 0.31 | 0.45 |
| Min | 0.83 | 29.65 | 59.43 | 0.91 | 29.06 | 59.00 |
| 25th percentile | 0.95 | 29.89 | 59.80 | 1.00 | 29.71 | 59.59 |
| 50th percentile | 0.97 | 29.98 | 59.94 | 1.03 | 29.99 | 59.96 |
| 75th percentile | 1.02 | 30.09 | 60.10 | 1.08 | 30.10 | 60.21 |
| Max | 1.10 | 30.78 | 60.43 | 1.23 | 30.52 | 60.82 |
| Range | 0.27 | 1.13 | 1.00 | 0.32 | 1.46 | 1.82 |

*60 tests for each set dose

Figure showing bar chart with the following data labels:

FP 40 IU: 6% | 24% | 38% | 22% | 10%
NGFP 40 IU: 4% | 24% | 48% | 24% | *
FP 60 IU: 22% | 46% | 10% | 14% | 6% †
NGFP 60 IU: 2% | 14% | 46% | 30% | 8% *

100   50   0   50   100
Percentage of patients rating as postive or negative
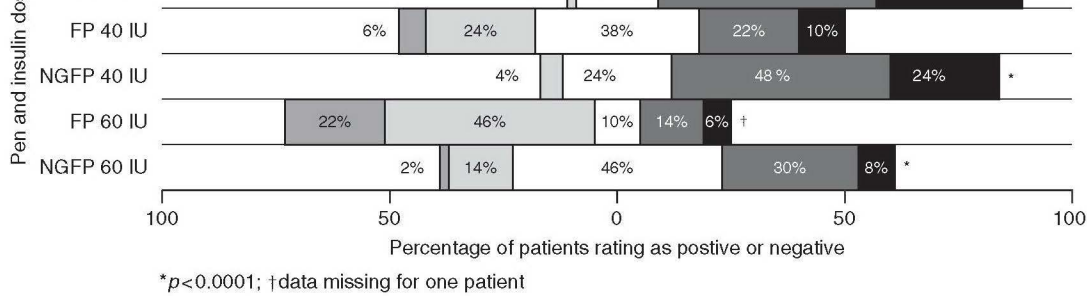
*p<0.0001; †data missing for one patient

**Figure 1.** *Patient perception of FP and NGFP injection force when injecting 20 IU, 40 IU and 60 IU of insulin aspart.*
*p < 0.0001 between pens; responses compared using likelihood ratio chi-square test*

One aim of this study was to confirm that the design changes had reduced the injection force of NGFP. The mean injection force for all NGFPs was 30% lower than the mean value for FPs. The maximum and minimum injection forces measured with 20 NGFPs (10.63–18.57 N) were consistently lower than the maximum and minimum injection forces measured with 20 FPs (15.35–19.99 N), therefore NGFP does have the desired reduced injection force. A lower injection force is generally preferred by patients simply because the lower the force required for injection, the easier it is to inject the insulin dose. This is particularly important in patients with impaired manual dexterity[20–22]. To test if the reduction in injection force with NGFP had an actual benefit to the end-user, the results from the user-preference study were included here. In this user-preference study, patients had a better perception of the injection force of NGFP than FP at all doses tested (nearly twice as many patients rated the injection force as 'good' or 'very good' with NGFP compared to FP). Not only does this suggest that the reduced injection force is perceived as an improvement by patients, but it also contributed to three out of four patients finding NGFP 'simpler and more comfortable' to use. However, a limitation of this study is the fact that NGFP has not been tested in routine clinical practice, and whether this preference is maintained in everyday use will need to be investigated.

With the increased use of insulin pens[23], a wider variety of patients will gain more experience with a range of pens. Different patient populations will have different specific demands and the importance of various pen features will vary from patient to patient. Several studies have investigated the reasons for patient preference for pens over vial and syringe[8–10,24–27]. For example, in a study of insulin users and non-users, social acceptability and ease of use were the most important factors for preference for pens[10]. In a study of FP versus vial and syringe, patients preferred FP due to improvements in convenience, flexibility, perceived clinical efficacy and quality of life[26]. The changes to NGFP are designed to enhance the preferred features of FP further and this report suggests that NGFP is rated as 'simpler and more comfortable' to use than FP, because it delivers the same accurate and reliable doses of insulin at high and low doses under a variety of everyday conditions, but with a considerably lower dose force.

## Conclusion

The modifications made to NGFP have resulted in a significant 30% reduction in injection force compared with FP. These changes have contributed to NGFP being considered more 'simple and comfortable' to use by patients. Importantly, the dose accuracy of NGFP is at least as good as FP, and our study suggests that NGFP may actually be significantly more accurate and precise than FP – deviation from set doses and the variance in the delivered dose were small with both pens but smallest with NGFP. Although the NGFP has not been tested in everyday use, this study suggests that the changes made are likely to enhance patient comfort and aid accurate insulin dosing.

## Acknowledgements

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