ORIGINAL ARTICLE

Study on the Dosing Accuracy of Commonly Used Disposable Insulin Pens

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Abstract

Background: Improved patient comfort and optimal glycemic control have led to the widespread use of insulin pens, particularly in Europe. Most of the former studies on the dose accuracy of insulin pens included only a small number of doses and pens. In extension to our previous large-scale study testing the dosing accuracy following a randomized dosing sequence with each pen, the present study was more directed toward the dose accuracy for one specific dose dispensed repeatedly with the same pen. This is the first study providing detailed comparative data on the accuracy of repeated dose delivery with prefilled disposable insulin pens at low, middle, and high doses, dispensed over the entire pen volume.

Materials and Methods: In total, 15 previously unused insulin pens from two lots of each pen type (SoloSTAR® [sanofi-aventis, Paris, France], FlexPen® [Novo Nordisk A/S, Bagsværd, Denmark], Next Generation FlexPen [Novo Nordisk], and KwikPen™ [Eli Lilly, Indianapolis, IN]) were used to deliver 5-unit (low), 30-unit (middle), and 60-unit (high) doses, respectively, dispensed four times from each pen in a nonrandomized manner. Actual doses were determined gravimetrically taking the density of the respective insulin into account and were evaluated according to the guidelines (DIN EN ISO 11608-1:2000) of the International Organization for Standardization (ISO).

Results: All tested insulin pens met the requirements for accuracy with none of the single values being outside the defined range of the ISO recommendations (1 ± 1 units, 30 ± 1.5 units, and 60 ± 3 units, respectively).

Conclusion: The present study demonstrated a consistent and accurate dose delivery at all dosage levels for all tested insulin pens, with no clinically relevant differences among the products.

Introduction

Since the first insulin pen was introduced in 1985, insulin pens have significantly contributed to improved patient comfort and optimal glycemic control.[1] They offer several advantages over the traditional vial-and-syringe method, such as reduced pain during injection, discretion of use, easy portability, and fewer claims for hypoglycemic events.[2–4] Because of these advantages the use of insulin pens is widespread, particularly in Europe.[1]

As patients rely heavily upon device accuracy to administer the correct amount of insulin, the accuracy of insulin pens is an important issue. Insulin pens are available in two types: reusable and disposable insulin pens. The most commonly used disposable pens include the SoloSTAR® (SR) (sanofi-aventis, Paris, France), the FlexPen® (FP) and Next Generation FlexPen (NGFP) (Novo Nordisk A/S, Bagsværd, Denmark), and the KwikPen™ (KP) (Eli Lilly, Indianapolis, IN). Several studies have been dedicated to comparing the dosing accuracy among disposable insulin pens. In general, these studies verified the accurate dosing of disposable insulin pens, even when compared with the vial and syringe.[5–13] However, they followed different study designs with regard to the number of pens and doses tested, yielded partly contradicting results, and, with the exception of the study of Krzywon et al.,[11] did not extend over the whole dosing range but mainly concentrated on testing 10-unit and 30-unit doses. Therefore our first study was dedicated to comparing the dose accuracy of SR, FP, NGFP, and KP over a wide dosing range (1 unit, 10 units, 30 units, 60 units, and 80 units) dispensed in random order.[11]

The dose regimen of patients with diabetes may require a roughly constant daily dose of their basal insulin. For that reason the following study was aimed to complement our previous study by investigating the dose accuracy of the SR,

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with the same pen.

Materials and Methods

SR and FP were bought from German pharmacies. KP and NGFP were bought in pharmacies in the United States and France. An overview of the included insulin pens and corresponding needles is given in Table 1. The needles were applied according to the manufacturers' recommendation.

In total, 45 previously unused insulin pens from two lots of each pen type (15 pens of each pen type for each dosage level, respectively) was used for the study. Each of the low (5-unit), middle (30-unit), and high (60-unit) doses was dispensed four times from each pen in a nonrandomized manner according to the dose delivery scheme presented in Figure 1. Between these recorded doses intermediate doses were dispensed without recording the mass to ensure dose dispensing over the entire pen volume.

The individual insulin pens were operated according to the manufacturers' instructions. Prior to starting the sequence of measurements, one to two priming doses of 2 units were discarded. If still no drops were seen at the top of the needle, the priming dose was repeated until this was the case. Following the manufacturers' recommendation the priming doses of the KP were repeated until a visible stream of insulin left the needle. All measurements were performed by a single investigator to eliminate potential user variability. As per manufacturers' instructions the plunger was kept pressed down for 10 s, 6 s, and 5 s in the case of SR, both FP and NGFP, and KP, respectively, after each dose to ensure that all the dialed dose had been expelled. Each dose was deposited in a beaker containing a 0.5–1 cm layer of liquid paraffin, whereas the pen was held close to the surface of the paraffin layer. In case an insulin drop remained at the tip of the needle at the end of the relaxation time, this drop was stripped off at the paraffin surface, taking care that the needle did not strike the paraffin. Afterward the dose was weighed immediately using an analytical balance (model XP205/M; Mettler Toledo AG, Gießen, Germany), which has an accuracy of 0.00001 g. The balance was zeroed before each dose of insulin was deposited and weighed. The weights were corrected for the specific density of each insulin formulation determined in the run-up to the study. For insulin glargine (SR), insulin detemir (FP and NGFP), and insulin lispro (KP), the density was determined to be 1.0036 g/cm^3, 1.00798 g/cm^3, and 1.00447 g/cm^3, respectively, using a DMA 4500 density meter (Anton Paar GmbH, Bruchköbel, Germany). For each dose

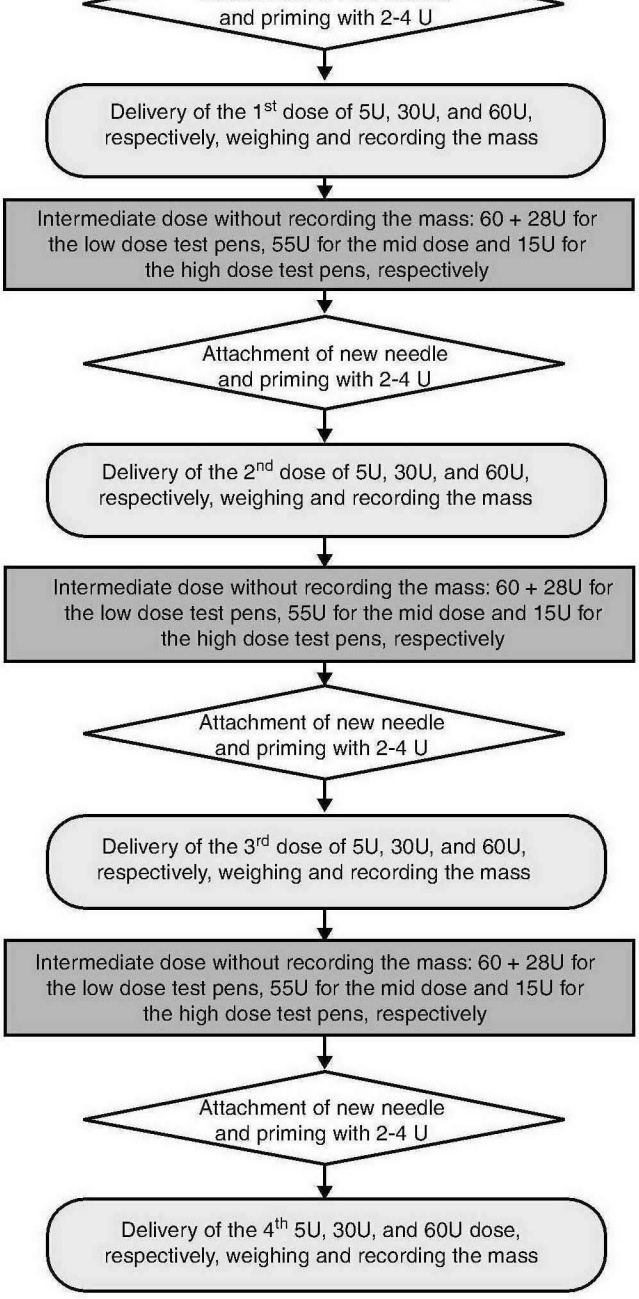

FIG. 1. Dose delivery scheme for each pen.

TABLE 1. INSULIN PENS AND CORRESPONDING NEEDLES INCLUDED IN THE STUDY

Insulin pen	*Manufacturer*	*Batch*	*Insulin*	*Needles*
SoloSTAR	sanofi-aventis	40U142 40U144	Glargine	BD Micro-Fine (0.25 mm [31 gauge] × 8)
FlexPen	Novo Nordisk	VH 70047 VH 70215	Detemir	NovoFine (0.3 mm [30 gauge] × 8)
Next Generation FlexPen	Novo Nordisk	VH 70007 VH70235	Detemir	NovoFine (0.3 mm [30 gauge] × 8)
KwikPen	Eli Lilly	A 477063 A 463790C	Lispro	BD Micro-Fine (0.25 mm [31 gauge] × 8)

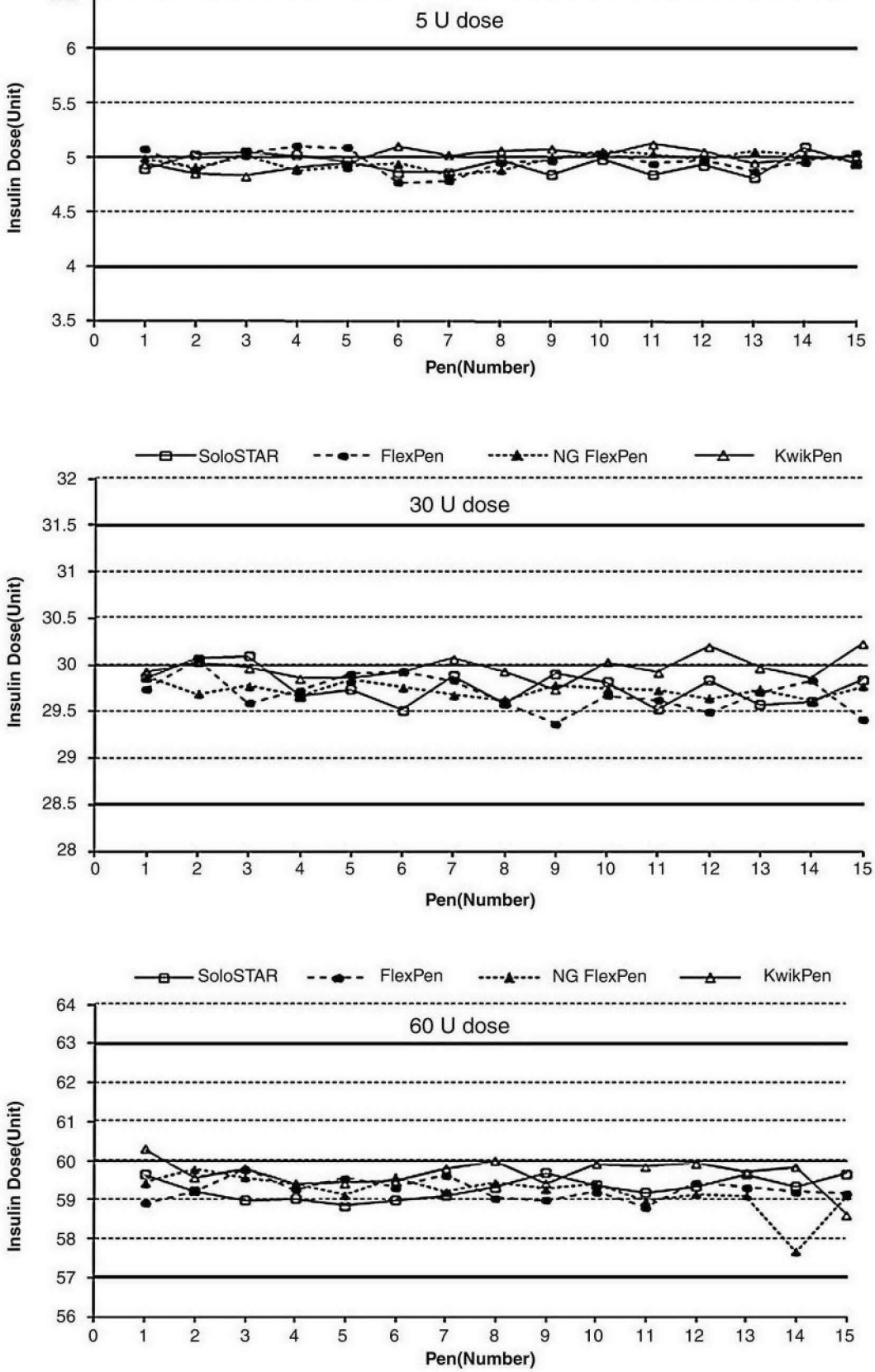

FIG. 2. Distribution of the average actual doses according to pen and dosage level ($n=4$). Bold lines represent the International Organization for Standardization limits, and the midline represents the target dose. NG, Next Generation.

dation before dose delivery. The whole study was carried out under Good Manufacturing Practice conditions and was additionally documented by video.

The evaluation of dose accuracy was based on the guidelines (DIN EN ISO 11608-1:2000) of the International Organization for Standardization (ISO).[14] The statistical tolerance interval $[\bar{x} \pm (k \cdot s)]$ (see Results) for each pen should lie within the upper and lower acceptance limits for each dosage level. According to the ISO guidelines the calculated statistical tolerance limit should not deviate from the target dose by more than 1 unit for the delivery of 5 units and not by more than 5% for the delivery of 30 units and 60 units. For the individual doses tested in this study the acceptance limits are 5 ± 1 units (4.0–6.0 units), 30 ± 1.5 units (28.5–31.5 units), and 60 ± 3 units (57–63 units). In addition, the arithmetic average of the actual doses, the SD, the coefficient of variation, and the average deviation in units and percentage from the target dose were calculated.

Results

According to the delivery scheme 60 doses were gravimetrically measured at each dosage level for each pen type, and the actual dose was calculated on the basis of the delivered masses and the density of the insulin solution. In general, the 5-unit doses were equally distributed around the target dose, whereas most of the 30-unit and almost all of the 60-unit doses were found to be below the target dose (Fig. 2). However, none of the tested insulin pens showed any trend toward increasing or decreasing doses with repetitive dosing.

Despite the high number of doses measured (720 in total, 180 per pen model) the study demonstrated a consistent and accurate dose delivery at all dosage levels for all tested insulin pens with none of the single values outside the specified limits recommended by ISO.

The arithmetic average of the actual doses, the SD, and the coefficient of variation, as well as the average deviation in units and the average relative percentage deviation from the target dose, are summarized in Table 2.

dose. For all tested insulin pens the average deviation of the actual dose from the target dose was below 2% at all tested dosage levels. The average deviations from the target dose ranged between −1.14% and −0.06% at 5 units, between −1.01% and −0.11% at 30 units, and between −1.32% and −0.55% at 60 units. Moreover, only marginal differences between the tested insulin pens in the reproducibility of dose delivery were detected. The highest variation was observed at the lowest dosage level of 5 units with values ranging between 3.1% and 4.1%, whereas at the higher dosage levels (30 units and 60 units) the coefficient of variation ranged between 0.5% and 0.9%.

The statistical tolerance intervals determined for each pen at each dosage level are presented in Figure 3. All calculated tolerance intervals $[\bar{x} \pm (k \cdot s)]$ were found to lie within the acceptance range for each dosage level for each pen, where $\bar{x}$ is the average value of the actual doses for each pen at each dosage level, s = SD, and k is the tolerance limit factor, which was found to be 2.670 on the basis of the 95% confidence interval for $n = 60$.[14]

Discussion

Six studies examined the comparable dosing accuracy of disposable insulin pens.[5–11] In general, dosing accuracy was found to be good in all studies. Two studies comparing the SR with the FP reported few doses outside the ISO limits for both pens.[5,6] However, the number of pens included in these studies was very small (eight pens and three pens, respectively, of each type) and did not meet the ISO recommendations. Therefore these data may not be considered robust. In fact, repeating the study of Asakura et al.[6] on a 10-fold higher number of pens (30 pens each) revealed comparable accuracy of the SR and the FP with no single value of the 2,280 doses measured being outside the ISO limits.[8] Similar good results within the ISO limits were obtained for the NGFP, when comparing it with the FP.[9] Comparing the SR with the NGFP revealed good performance of both pens but reported few doses outside the ISO limits for both pens.[10] All the above-

Table 2. Overview on the Average of the Actual Doses, the Standard Deviation, the Coefficient of Variation, the Average Deviation in Units, and the Average Relative Percentage Deviation from the Target Dose for All Pens at Each Dosage Level

Pen	Target dose (units)	Actual dose			Average deviation (units)	Average relative deviation (%)
		Average dose (units)	SD (units)	CV%		
SR	5	4.943	0.153	3.1	−0.057	−1.14
FP		4.972	0.202	4.1	−0.028	−0.57
NGFP		4.969	0.188	3.8	−0.031	−0.62
KP		4.997	0.160	3.2	−0.003	−0.06
SR	30	29.769	0.253	0.8	−0.231	−0.77
FP		29.698	0.275	0.9	−0.302	−1.01
NGFP		29.729	0.210	0.7	−0.271	−0.90
KP		29.968	0.215	0.7	−0.032	−0.11
SR	60	59.283	0.357	0.6	−0.717	−1.19
FP		59.247	0.324	0.5	−0.753	−1.26
NGFP		59.206	0.503	0.9	−0.794	−1.32
KP		59.667	0.517	0.9	−0.333	−0.55

CV, coefficient of variation; FP, FlexPen; KP, KwikPen; NGFP, Next Generation FlexPen; SR, SoloSTAR.

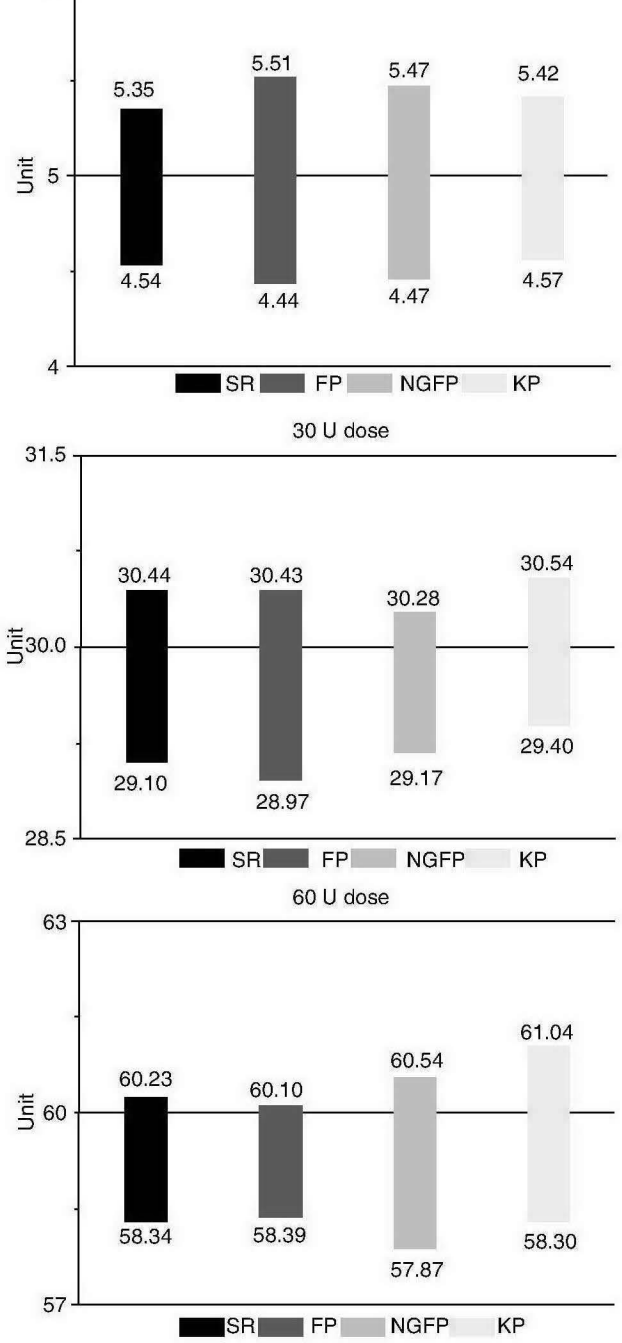

FIG. 3. Tolerance intervals for each pen at each dosage level. Bold lines represent the International Organization for Standardization limits, and the midline represents the target dose. FP, FlexPen; KP, KwikPen; NGFP, Next Generation FlexPen; SR, SoloSTAR.

mentioned studies included only a small number of doses and pens. In terms of an overall assessment of the dosing accuracy we conducted the first comparable study on a large scale including the most common insulin pens, SR, FP, NGFP, and KP, covering the low (1 unit), the middle (30 and 40 units), and the high (60 units) dosage levels for all pens in addition to the 80-unit dosage level for the SR in line with ISO guidelines.[11]

carried out so far revealed an excellent dosing accuracy for all tested insulin pens, with none of the single values (1,260 in total) at all dose levels being outside the defined range of the ISO recommendation. Previously reported dosing outside the ISO limits[5,6,10] could not be verified in this study.[11]

Following the ISO recommendation, the 1-unit dosage level should have been chosen for the low dosage level for all pens and the 40-unit and 80-unit dose as middle and high doses, respectively, for SR. Our current study assessed the dosing accuracy at the 5-unit (low), 30-unit (middle), and 60-unit (high) dosage levels for all pens, to enable comparability with previously published studies and because of the greater clinical relevance of the 5-unit dose compared with the 1-unit dose. The results obtained represent the dosing accuracy in the hands of a professional and do not take into account variabilities that may be introduced by users with diabetes in daily practice.

All tested insulin pens revealed an excellent repetitive dosing accuracy in the low, middle, and high dosage levels, thus assuring dose accuracy over the whole insulin pen. The tolerance limits defined by the ISO standards were met by all pens at all dosage levels. No single dose from SR, FP, NGFP, and KP at any dosage level was delivered outside the prespecified limits of the ISO guidelines. Again, previously published data that reported individual doses below the ISO limit for the SR, FP,[5,6] and NGFP[10] could not be verified. For all pens at all dosage levels only minor deviations from the target dose not exceeding 1.32% were observed. Being well within the defined ISO limits, these deviations may be regarded negligible in daily practice.

The comparable dosing accuracy of all insulin pens revealed in this study confirms the results of our earlier study using a randomized dosing sequence[11] and the results of Penfornis and Horvat,[8] demonstrating comparable dosing accuracy of SR and FP at the 5-unit and 30-unit dosage level. The outcome of this study is also in line with a clinical study carried out by Friedrichs[15] demonstrating comparable dosing accuracy for both SR and FP when used by device-naive subjects.

Conclusions

The present study reveals similar repetitive dosing accuracy for the tested insulin pens SR, FP, NGFP, and KP. None of the four insulin pens delivered at the low, middle, and high dosage level doses outside the prespecified limits of the ISO guidelines. Existing marginal differences among the pens in the deviation of the actual doses from the target dose are negligible in daily practice.

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Author Disclosure Statement

T.v.d.B. is an employee of sanofi-aventis. M.K., M.S.-Z., M.A.-T., and U.F. declare no competing financial interests. T.v.d.B. was involved in the design of the present study. M.K., M.S.-Z., and M.A.-T. were responsible for the realization/

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