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ORIGINAL ARTICLES

Dose Accuracy and Injection Force of Disposable Pens Delivering Pramlintide for the Treatment of Diabetes

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Abstract

Background:

The pen injection format, typically used for insulin administration, has been adapted for the injectable, noninsulin diabetes therapy pramlintide. Administered before major meals, pramlintide therapy requires two to four injections/day in addition to the patients' usual insulin injections. The dose accuracy and injection force was determined for the 60 and 120 μg pramlintide pens.

Methods:

Dose accuracy testing was conducted at two sites on multiple 60 μg (15, 30, and 60 μg doses) and 120 μg pens (60 and 120 μg doses) at prespecified temperatures (5–40 °C) and humidities (0–75%) using 29 G half-inch needles. All pens were stabilized under testing conditions for 4 h prior to testing. One site used a compression load cell (Zwick device) to test pens; one site performed tests manually.

Injection-force testing was conducted at one site on multiple 60 and 120 μg pens at multiple temperatures (18–28 °C) and humidities (25–75%) using 29 and 31 G half-inch needles and an injection speed of 150 m/min. Injection-force testing was performed using a Zwick device.

Results:

Dose accuracy for all pens tested, regardless of location, reproducibly met/exceeded acceptance criteria. Mean percentage of dose accuracy was 96.04 to 102.45% [standard deviations (SDs) 0.3 to 1.4 μg] for the 60 μg pen and 98.16 to 101.83% (SDs 0.4 to 2.5 μg) for the 120 μg pen. The average injection force across both pens did not exceed 7 N regardless of needle size.

Conclusions:

High dose accuracy and low injection force were observed for the 60 and 120 μg pens under a variety of conditions.

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Abbreviations: (ISO) International Organization for Standardization, (RH) relative humidity, (SD) standard deviation

Keywords: accuracy, hyperglycemia, pramlintide, reproducibility, type 1 diabetes, type 2 diabetes

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Introduction

The first pen injection device was launched in 1985[1] for the administration of insulin to patients with type 1 or advanced type 2 diabetes. Since then, pens have continued to gain in popularity, primarily outside the United States; however, pen use in the United States now appears to be increasing.[1]

Over the years, pens have been refined to improve accuracy and ease of use for self-injection. Pen properties associated with improved ease of use include portability and ease of reading, ease of adjustment, ergonomic design, sturdiness, and differentiation between multiple pens for patients using more than one injectable medication.[1] Some pens have additional safety features such as insufficient remaining dose stops that prevent users from receiving incomplete doses[2] and audible or tactile feedback to ensure complete dose delivery.[1] Ease of use is an important device parameter for the patient who must inject medication multiple times per day indefinitely and may improve medication adherence.[1] One aspect of "ease of use" is how much force is required by the patient to inject medication. Low injection force pens allow patients to inject the full dose by applying a low and steady pressure without experiencing hand or grip fatigue.[1] By increasing dosing accuracy, the pen injectors developed for insulin have helped reduce the incidence of hypoglycemia and hyperglycemia.[1]

Continuing refinement of the pen has contributed to growing acceptance by patients. A survey of studies between 1980 and 2008 assessing patient-reported outcomes of pen versus vial and syringe showed substantial preferences for the pen.[3] Of 29 studies assessing patient preference, >66% of patients in 28 studies preferred the pen; in 8 of 9 studies assessing pain, >50% of patients said the pen caused less pain; and in 10 of 12 studies assessing acceptability, >75% of patients rated the pen as more acceptable than vial and syringe.[3] The pen apparatus may be disposable or refillable.[4] Disposable pens are used until the drug cartridge is empty, and then the entire unit is disposed. Durable (refillable) pens are used repeatedly, and spent drug cartridges are replaced with new ones as needed. Luijf and DeVries surveyed the literature (1998 to 2009) relative to pen accuracy and preference and found that pen devices had greater accuracy than a vial and syringe device, especially at low doses (<5 IU).[5]

Pramlintide is an injectable therapy for patients with type 1 and type 2 diabetes who use mealtime insulin and who are not achieving desired glycemic goals despite optimized insulin therapy.[6] The usual dose for patients with type 1 and type 2 diabetes is 60 and 120 μg, respectively, although smaller doses of 45, 30, or 15 μg (type 1 patients) and 60 μg (type 2 patients) may be used. Pramlintide is an analog of the naturally occurring hormone amylin, which is cosecreted from the pancreatic β cells with insulin in response to a meal. Patients with diabetes are deficient in both insulin and amylin. Pramlintide, like amylin, slows gastric emptying, suppresses inappropriate postprandial glucagon secretion, and increases satiety. These effects complement those of insulin to help circulating glucose concentrations stay within the normal range, thus avoiding hyperglycemia and, over the long-term, lowering hemoglobin A1c.

In patients with type 1 or type 2 diabetes, pramlintide is injected just before a meal, which is defined as food intake containing ≥250 kcal or ≥30 g of carbohydrate.[6] Unlike insulin, pramlintide dosing does not vary based on body weight or the caloric/carbohydrate content of a meal beyond the ≥250 kcal/≥30 g carbohydrate threshold. Patients using pramlintide require two to four injections per day (based on eating habits) in addition to their injections of rapid-acting insulin. Thus, a drug delivery system (pen) that increases ease of use and accuracy may be beneficial to patients.

This article describes the design features, dose accuracy, and dose injection force of the pramlintide pen delivery system.

Methods

Design Features

Two sets of dosing options are available for the pramlintide pen. The 60 μg pen delivers fixed doses of 15, 30, 45, and 60 μg; the 120 μg pen delivers fixed doses of 60 and 120 μg. Adjustable dosing allows patients to use less pramlintide if they better tolerate lower than higher doses or require gradual titration to improve tolerability. The fixed dose design differs from that used in insulin pens, which are designed to deliver a continuous drug dose across a wide range. Both pramlintide pens allow use of 29, 30, or 31 G type A needles, and the pens may be used

for up to 30 days, depending on dose size and injection frequency. The filled pen is stable between 2 and 42 °C, and patients are instructed to store the pens at 2–8 °C before first use, after which the pens may be stored from 2–8 °C up to 30 °C. Pens have a maximum diameter of 18.9 mm (~0.75 in.) and, when capped, a length of 158 mm (6.2 in.; **Figure 1**; data on file, Amylin Pharmaceuticals, Inc.). Three key design features help ensure a high level of dosing accuracy. A stroke sleeve moves the toothed rod forward by a precise distance when the dosage knob is depressed, and a guiding sleeve with interlocking teeth prevents the toothed rod from traveling backward (data on file, Amylin Pharmaceuticals, Inc.).

Dose Accuracy Protocol

Dose accuracy studies were performed at two different sites [Amylin Pharmaceuticals, Inc, San Diego, CA (site A) and Ypsomed AG, Burgdorf, Switzerland (site B)]. Both sites used International Organization for Standardization (ISO) guideline 11608-1, developed to test the "performance requirements regarding essential aspects" of pen injection devices.[7] The ISO testing criteria provides guidance on preconditioning and testing conditions, including temperature and humidity as well as dose accuracy requirements and statistical considerations. The preconditioning/testing conditions used in these experiments were within the specifications noted in ISO 11608-1. Pens were prepared for testing by attaching a new needle and performing the pen setup described in patient instructions (needle attachment and depression of pen dose knob until the expulsion of fluid was seen from the needle). At site A, each pen was placed in a Zwick device (Zwick/Roell Z2.5 tester with compression load cell; Ulm, Germany), and doses were expelled until the pen was completely emptied. A Zwick device measures the compression or tension force on a sample. The mass of expelled samples was determined using a Mettler SAG285 scale (0.01 mg resolution; Toledo, OH). Testing was conducted at 25 to 26 °C, with a relative humidity (RH) of 36% to 39%, using 29 G half-inch needles of a single lot. Five 60 μg pens were tested using the 30 and 60 μg dose, with 42 and 21 doses expelled/pen, respectively; five 120 μg pens were tested using the 60 and 120 μg dose, with 42 and 21 doses expelled/pen, respectively. Site B conducted dose accuracy testing manually under three different conditions: cold (5 ± 3 °C, no RH), standard (18 to 25 °C, 25–75% RH), and hot (40 ± 2 °C, 50 ± 10% RH) using 29 G half-inch needles of a single lot. Fifteen 60 μg pens were tested using the 15, 30, and 60 μg doses, with four doses expelled/pen; fifteen 120 μg pens were tested using the 60 and 120 μg doses, with four doses expelled/pen. At both sites, pens were stabilized under testing conditions for 4 h prior to testing. Data from the first (priming) dose of each pen were discarded from calculations. The conversion from mass to volume was $V_{measured} = G_{measured}/\rho$, where $V_{measured}$ is the volumetric measurement value for a given dose; $G_{measured}$ is the gravimetric measurements expressed in grams for a given dose; and ρ is density, expressed in grams per milliliter, 1.015 g/ml for pramlintide injection in cartridge. Acceptable dosing accuracy was defined as meeting or exceeding acceptance criteria described in section 9.2 of ISO 11608-1:2000(E).[7]

Injection Force Protocol

Injection force tests were conducted at site A only. Pens were prepared for testing by attaching a new needle and performing the pen setup described in patient instructions (needle attachment and depression of pen dose knob until the expulsion of fluid was seen from the needle). Testing was performed using 10 pens of both pen sizes using a Zwick device and was conducted at 18 to 28 °C and at 25 to 75% RH. Both 60 and 120 μg pens were tested using a 29 and 31 G half-inch needle. A standard injection speed of 150 m/min was used

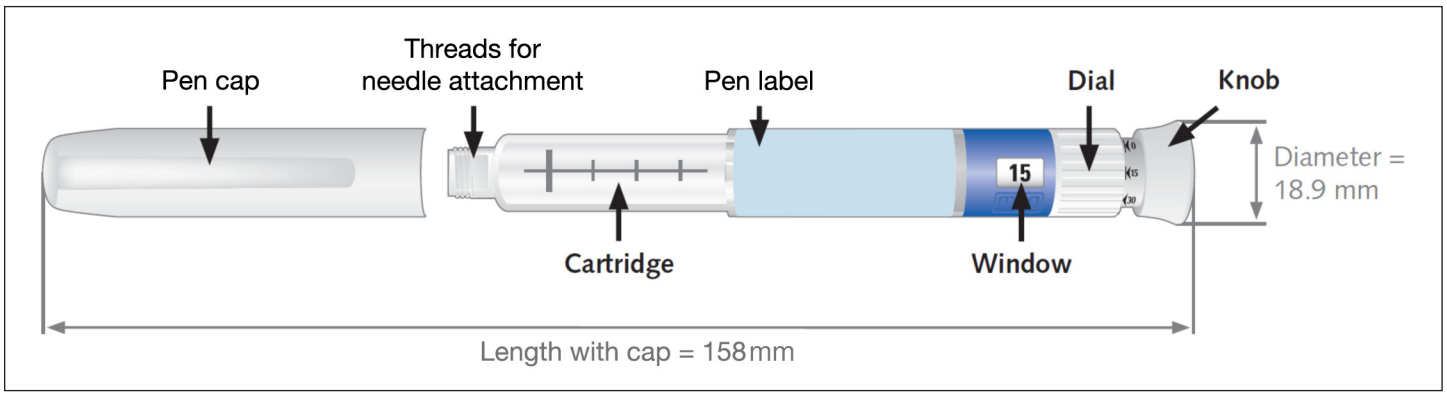

Figure 1. Pramlintide pen injection device.

for all tests, as it mimicked a typical injection time of approximately 2 s and made determination of peak injection force easier. Data from the first (priming) dose of each pen were discarded from calculations. Data for each pen/needle configuration consisted of three sets of two force tests. Each set of two force tests was preceded by one unmeasured force test and separated from the other force tests by six manual expulsions of drug so that data were collected from the beginning, middle, and end of the pen capacity. There are no established criteria for force testing.

Results

Dose Accuracy Results

Both 60 and 120 μg dose pens delivered accurate and reproducible doses at temperatures ranging from 5 to 40 °C and RH ranging from 0 to 75%. Different sites, testing protocols, operators, and dose sizes produced consistent dose accuracy results. All pens met or exceeded the ISO 11608-1:2000(E) criteria.[7]

At site A, the 60 μg pen delivered a 30.0 to 32.0 μg dose [overall mean percentage of dose accuracy 102.45%; standard deviation (SD) range 0.3 to 0.4] when the 30 μg dose was injected and delivered a 60.3 to 60.8 μg dose (overall mean percentage of dose accuracy 101.19%; SD range 0.4 to 0.8) when the 60 μg dose was injected. The 120 μg pen delivered a 59.5 to 61.3 μg dose (overall mean percentage of dose accuracy 100.41%; SD range 0.4 to 2.4) when the 60 μg dose was injected and delivered a 118.9 to 120.7 μg dose (overall percentage of dose accuracy 99.84%; SD range 0.4 to 1.5) when the 120 μg dose was injected (**Figure 2**). The variability of pen 4 (120 μg pen delivering a 60 μg dose) was greater than any other pen tested; however, it still met all pen release criteria (data not shown) as well as the ISO-11608-1 acceptance criteria.[7]

At site B, the 60 μg pen delivered a 14.4 to 14.9 μg dose (overall percentage of dose accuracy across all temperatures 98.34%; SD range 0.4 to 0.64) when the 15 μg dose was injected, a 28.9 to 29.6 μg dose (overall percentage of dose accuracy across all temperatures 97.96%; SD range 0.8 to 1.4) when the 30 μg dose was injected, and a 58.9 to 59.6 μg dose (overall percentage of dose accuracy across all temperatures 98.81%; SD range 0.6 to 0.7) when the 60 μg dose was injected. The 120 μg pen delivered a 58.9 to 61.1 μg dose (overall percentage of dose accuracy 100.26% across all temperatures; SD range 0.8 to 2.5) when the 60 μg dose was injected and delivered a 118.3 to 120.6 μg dose (percentage of dose accuracy 99.75% across all temperatures; SD range 1.1 to 2.3) when the 120 μg dose was injected (**Figure 3**).

Injection Force Results

The injection force values of all pens were similar regardless of the dose/needle combination used (**Figure 4**). The average injection force for the 60 μg pen (60 μg dose, 29 G needle) ranged from 4.1 to 6.6 N (SD range 0.2 to 0.3), with a maximum force ranging from 6.3 to 10.1 N; the average injection force for the 60 μg pen (60 μg dose, 31 G needle) ranged from 4.5 to 6.4 N (SD range 0.1 to 0.7), with a maximum force ranging from 6.8 to 9.5 N. The average injection force for the 120 μg pen (120 μg dose, 29 G needle) ranged from 3.2 to 6.5 N (SD range 0.2 to 0.6), with a maximum force ranging from 5.0 to 10.0 N; the average injection force for the 120 μg pen (120 μg dose, 31 G needle) ranged from 2.8 to 6.5 N (SD range 0.1 to 0.7), with a maximum force ranging from 4.3 to 9.6 N.

Discussion

The pramlintide pen device delivers a fixed dose of pramlintide for use as indicated by patients with type 1 or type 2 diabetes who use mealtime insulin. Its design is based on a general insulin pen template and incorporates several engineering elements to increase accuracy. These studies showed that patients who use the pen as directed will consistently receive the prescribed dose of pramlintide with accuracy.

The dose accuracy of the pramlintide pen across multiple sites, temperatures, RH, and operators, at both the minimum and maximum doses, was highly reproducible. Pen design, specifically the guiding sleeve, stroke sleeve, and the toothed rod, was viewed as key in producing accurate results across a variety of conditions and operators. The stroke sleeve moves the toothed rod forward by a precise distance when the dosage knob is depressed, and a guiding sleeve with interlocking teeth prevents the toothed rod from traveling backward. The dose accuracy was well within the ISO specifications set for pen injectors.

The average injection force for both configurations of the pramlintide pen was low, <7 N, and did not appear to be affected by needle size. The injection forces for the pramlintide pen were substantially lower than those observed for insulin pens that have reported injection forces ranging from approximately 10 to 25 N.[1] In a study comparing usability and patient preference for different pen injectors, patients preferred the pen with the lowest injection force.[8] Given that patients with diabetes will routinely inject medication multiple times per day

indefinitely, one could safely assume that a device that accurately delivers medication with a low injection force would be preferred.

The strengths of these testing protocols included testing the indicated doses under multiple conditions for the entire pen volume under highly controlled conditions. The primary weakness for injection-force testing was that only one injection speed was used. Greater dosing variability is expected with patient use based on the range of patient understanding regarding the injection process and the ability to accurately execute an injection.

The first insulin pen was launched in 1985, and currently, pens account for just over 50% of all insulin injectables worldwide.[1] The popularity of the pen compared to vial and syringe has grown because of increased dose accuracy, ease of use, and decreased cost. Most, if not all, pen development was done with insulin where the critical issue was dose accuracy so as to avoid hypoglycemia and hyperglycemia.[2] Numerous insulin studies have shown pens to be more accurate than vial and syringe, especially at doses <5 U.[9-12] Ease of use for pens encompasses multiple issues from the practical/ergonomic to the psychological, including ease of dose

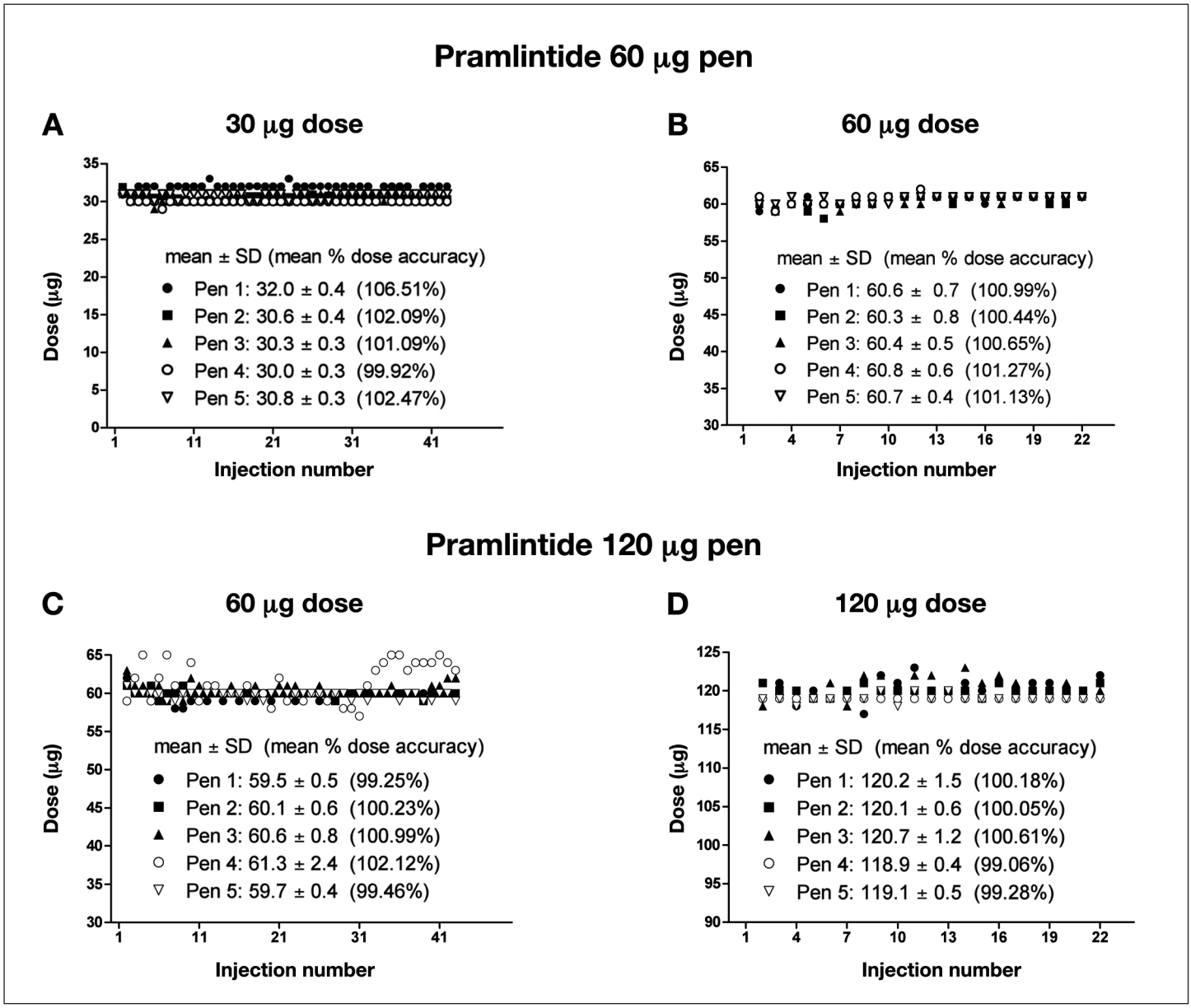

Figure 2. Dose accuracy, site **A**. Dose accuracy (mean dose ± SD, percentage dose accuracy) of the 60 μg pen to dispense **(A, B)** a 30 and 60 μg dose and of the 120 μg pen to dispense **(C, D)** a 60 and 120 μg dose using multiple pens. Temperature (25 to 26 °C), RH (36% to 39%), needle size (29 G), lot number, and operator were identical for all pens.

dialing/correction, large print dose displays, low injection force, portability, easy cartridge change, dose confirmation, and visual/tactile differentiation of different pens. The pen format also helps ease some of the stress encountered when the patient must adjust an established oral therapy to include an injectable therapy.[1] Medications and associated devices can also represent a substantial cost to the patient, especially when treating a chronic long-term disease. Cost analyses have shown that pen use reduced all-cause annual treatment costs by ~$1590/patient.[1] Pen use with insulin has been shown to reduce the incidence of hypoglycemia/hyperglycemia, which has not only substantial health ramifications, but also potentially significant associated costs.[1] A review of patient-reported

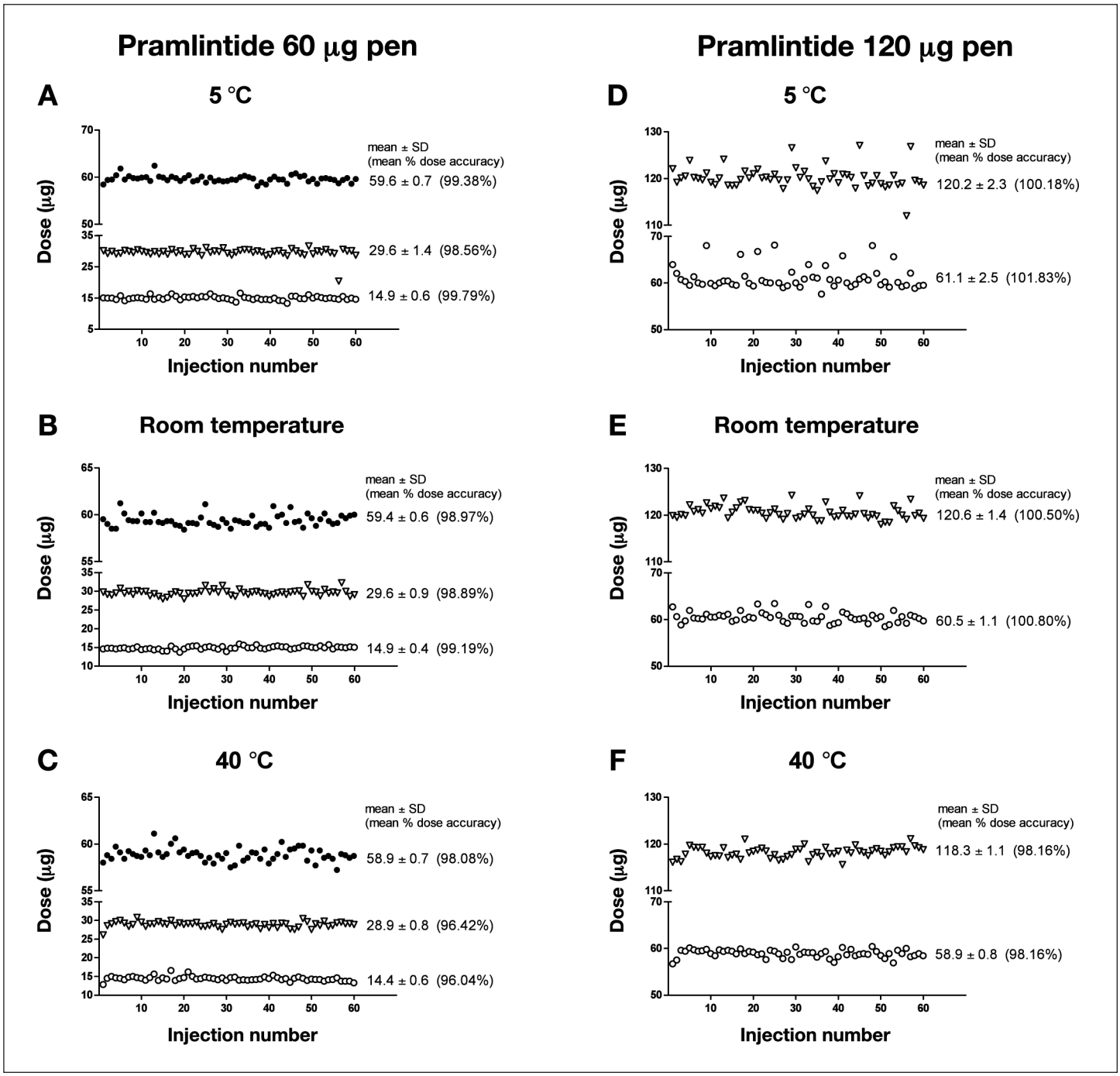

Figure 3. Dose accuracy, site **B**. Dose accuracy (mean dose ± SD, percentage dose accuracy) of the 60 μg pen to dispense a 15, 30, and 60 μg dose at **(A)** 5 °C and 0 RH, **(B)** room temperature and 25–27% RH, and **(C)** 40 °C and 50 ± 10% RH. Dose accuracy of the 120 μg pen (mean dose ± SD, percentage dose accuracy) to dispense a 60 and 120 μg dose at **(D)** 5 °C and 0 RH, **(E)** room temperature and 25–27% RH, and **(F)** 40 °C and 50 ± 10% RH. Testing personnel, needle size (29 G), and lot number were identical for all pens.

outcomes for pen versus vial and syringe studies between 1980 and 2008 showed highly favorable results for the pen. Improvement in areas such as reduced pain with injections, treatment satisfaction, and treatment convenience for the pen versus vial and syringe ranged from 50 to 100%.[3] Improved patient outcomes can help patient adherence, which is of paramount importance in achieving and maintaining optimal health within disease parameters, and helps decrease overall costs.[1,13]

Despite the positive attributes of the pen, use of the vial and syringe format for delivery of injectable diabetes medications is still predominant in the United States. This is surprising given that the vial and syringe format

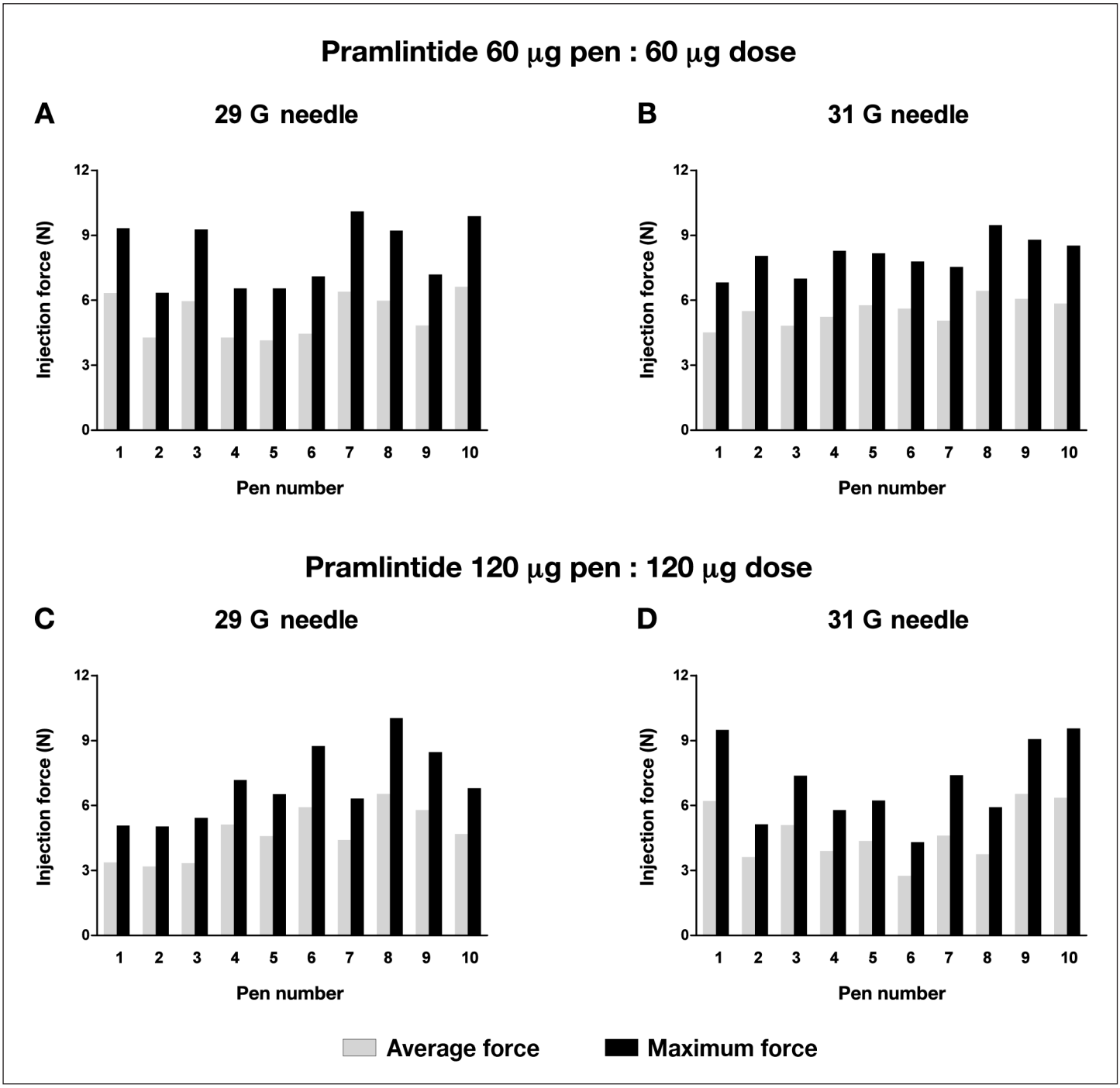

Figure 4. Injection force measurements, site **A**. Injection force required for the 60 μg pen to dispense a 60 μg dose using **(A)** a 29 G needle and **(B)** a 31 G needle and the 120 μg pen to dispense a 120 μg dose using **(C)** a 29 G needle and **(D)** a 31 G needle. Injection velocity (150 m/min), temperature (18 to 28 °C), RH (25% to 75%), and operator were identical for all pens.

is associated with poor dose accuracy, fear of injections,[14,15] inconvenience,[16] lack of social acceptance,[17] and poor accuracy when self-mixing insulin.[18] These negative attributes often result in a profound psychological resistance in health care providers and patients to use injectables such as insulin.

The Food and Drug Administration Human Factors Guidelines for Medical Devices recognizes that errors associated with the incorrect use of medical devices can pose a hazardous situation for the patient and potentially others.[19] Medical devices are often complex and may be used under stressful conditions. These devices are also used by patients whose comprehension of the disease/device may vary widely.

The design of the pramlintide pen addresses some important human factors issues by combining many features seen in insulin pens such as ease of use, ergonomic design, color coding, and convenience with fixed dosing and improved dose accuracy while maintaining a low injection force. While dosing approaches differ between pramlintide and insulin (no insulin-like titration is required for pramlintide), all pen devices are required to adhere to a standard of accuracy. Improved accuracy as well as a low injection force requirement may alleviate some of the anxiety associated with introducing a new therapy—for health care providers and patients alike.

Conclusion

A high degree of dose accuracy and low injection force make the pramlintide pen an attractive alternative to vial and syringe when administering pramlintide.

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Disclosures:

All Amylin-affiliated authors own stock in Amylin Pharmaceuticals, Inc.

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Ypsomed AG, Burgdorf, Switzerland, developed and supplied the pen device as well as contributed to the experimental data described in this article.

References:

1. Clarke A, Spollett G. Dose accuracy and injection force dynamics of a novel disposable insulin pen. Expert Opin Drug Deliv. 2007;4(2):165–74.
2. Klonoff DC. The pen is mightier than the needle (and syringe). Diabetes Technol Ther. 2001;3(4):631–3.
3. Molife C, Lee LJ, Shi L, Sawhney M, Lenox SM. Assessment of patient-reported outcomes of insulin pen devices versus conventional vial and syringe. Diabetes Technol Ther. 2009;11(8):529–38.
4. Diabetes Health. Product reference guide 2010. http://www.diabeteshealth.com/media/pdfs/PRG2010/2-Insulin_Pens_Chart-Diabetes_Health_2010.pdf. Accessed July 13, 2010.
5. Luijf YM, DeVries JH. Dosing accuracy of insulin pens versus conventional syringes and vials. Diabetes Technol Ther. 2010;12 Suppl 1:S73–7.
6. SYMLIN (pramlintide acetate) injection. Prescribing Information. Amylin Pharmaceuticals Inc., San Diego, CA. Revised July 2008. https://www.symlin.com/pdf/SYMLIN-pi-combined.pdf. Accessed September 8, 2010.
7. International Organization for Standardization. Pen-injectors for medical use—Part 1: pen-injectors—requirements and test methods. ISO 11608-1:2000(E). http://www.iso.org/iso/catalogue_detail.htm?csnumber=19545. Accessed September 8, 2010.
8. Haak T, Edelman S, Walter C, Lecointre B, Spollett G. Comparison of usability and patient preference for the new disposable insulin device SoloStar versus FlexPen, Lilly disposable pen, and a prototype pen: an open-label study. Clin Ther. 2007;29(4):650–60.
9. Gnanalingham MG, Newland P, Smith CP. Accuracy and reproducibility of low dose insulin administration using pen-injectors and syringes. Arch Dis Child. 1998;79(1):59–62.
10. Lteif AN, Schwenk WF. Accuracy of pen injectors versus insulin syringes in children with type 1 diabetes. Diabetes Care. 1999;22(1):137–40.
11. Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO. Inadequate suspension of neutral protamine Hagendorn (NPH) insulin in pens. Lancet. 1999(9190);354:1604–7.
12. Pearson TL. Practical aspects of insulin pen devices. J Diabetes Sci Technol. 2010;4(3):522–31.
13. Selam JL. Evolution of diabetes insulin delivery devices. J Diabetes Sci Technol. 2010;4(3):505–13.
14. [Fear of the injection must not be an argument. Every second type 2 diabetic patient needs insulin.] MMW Fortschr Med. 2002;144(49):60.
15. Wagner J, Malchoff C, Abbott G. Invasiveness as a barrier to self-monitoring of blood glucose in diabetes. Diabetes Technol Ther. 2005;7(4):612–9.
16. Keith K, Nicholson D, Rogers D. Accuracy and precision of low-dose insulin administration using syringes, pen injectors, and a pump. Clin Pediatr (Phila). 2004;43(1):69–74.

17. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther. 2004;26(9):1498–505.

18. Bell DS, Clements RS Jr, Perentesis G, Roddam R, Wagenknecht L. Dosage accuracy of self-mixed vs premixed insulin. Arch Intern Med. 1991;151(11):2265–9.

19. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. About human factors. *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/HumanFactors/ucm119185.htm*. Accessed February 4, 2010.