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ORIGINAL ARTICLE

Novel Methodology to Determine the Accuracy of the OmniPod Insulin Pump: A Key Component of the Artificial Pancreas System

Howard Zisser, M.D.,[1] Marc Breton, Ph.D.,[2] Eyal Dassau, Ph.D.,[3] Kateryna Markova, M.D.,[1] Wendy Bevier, Ph.D.,[1] Dale Seborg, Ph.D.,[3] and Boris Kovatchev, Ph.D.[2]

Abstract

Background:

This article describes two novel and easy approaches for assessing the accuracy of insulin pumps as implemented within the artificial pancreas system. The approaches are illustrated by data testing the OmniPod Insulin Management System at its lowest delivery volume (0.05 U) and at doses of 0.1, 0.2, 1, and 6U.

Method:

In method 1, a pipette, digital microscope, and imaging software were used to measure average bolus delivery on a linear scale for multiple volumes. In method 2, a digital microscope and imaging software were used to measure the volume of a spherical bolus of 0.05 U of insulin.

Results:

Bench testing results using the two novel methods demonstrated that the OmniPod is extremely accurate, with a relative error ranging from -0.90% to +0.96% for all measured doses (0.05, 0.1, 0.2, 1, and 6 U). In method 1, at target bolus dose of 0.05 U, the mean delivered dose (± standard deviation) was 0.0497 ± 0.003 U, 0.099 ± 0.005 U at 0.1 U, 0.2 ± <1e-5 U at 0.2 U, 1.001 ± 0.018 U at 1 U, and 6.03 ± 0.04 U at 6 U. In method 2, at target bolus dose of 0.5 µl, the mean delivered dose for both OmniPods was 0.505 ± 0.014.

Conclusions:

Both methods confirmed a high degree of accuracy for the OmniPod insulin pump. These techniques can be used to estimate delivery volume in other infusion pumps as well.

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Author Affiliations: [1]Sansum Diabetes Research Institute, Santa Barbara, California; [2]Center for Diabetes Technology, University of Virginia, Charlottesville, Virginia; and [3]University of California, Santa Barbara, Santa Barbara, California

Abbreviations: (AE) adverse event, (APS) artificial pancreas system, (DKA) diabetic ketoacidosis, (FDA) Food and Drug Administration, (SD) standard deviation

Keywords: accuracy, artificial pancreas, bolus, dose, insulin pump, method, OmniPod, pipette

Corresponding Author: Howard Zisser, M.D., Sansum Diabetes Research Institute, 2219 Bath St., Santa Barbara, CA 93105; email address hzisser@sansum.org

Introduction

An initiative to improve the safety of infusion pumps was announced by the Food and Drug Administration (FDA) in April 2010 following 56,000 adverse event (AE) reports and 87 infusion pump recalls over the previous 4 years, mainly involving in-hospital intravenous infusion pumps. Alarmingly, 14 of the recalls were class I, defined as a reasonable probability that the use of the device will cause serious adverse health consequences or death. These issues were observed across different manufacturers, types of pumps, and use environments. The most common types of reported problems have been associated with software defects, user interface issues, and mechanical or electrical failures. Increasing concerns by the FDA resulted in new requirements being established for the pump manufacturers.[1]

Insulin pumps make up a small portion of all medical infusion pumps, although their number is increasing by approximately 10% per year,[2] following the increase in diabetes worldwide. In May 2008, the FDA published the results of a retrospective 10-year study (1996–2005) of AE reports of insulin and analgesia pumps by adolescents (12 to 21 years old).[3] There was a total of 1594 AE reports regarding insulin pump use. Reported events included injuries (65.1%), malfunctions (33.1%), "other events" (0.9%), and death in 13 patients (0.8%). Reported deaths were related to either hyperglycemic or hypoglycemic complications (n = 5), diabetic ketoacidosis (DKA; n = 3), seizure (n = 1), coma (n = 1), or nonindicated cause (n = 3). Hyperglycemia was reported in 987 (61.9%) events, of which 46.6% involved DKA. Overdelivery of insulin and/or hypoglycemia events were reported in 167 (10.5%) reports. Primary issues causing the events were reported as educational faults, noncompliance, and issues during activities such as sports. Further perfection of technology and design of insulin pumps is required in order to assure ease of use, safety, and compliance. Of note is the fact that there is no good comparison group for AEs related to the use of insulin vials/syringes/pens. A majority of the "pump" events may not have anything to do with the pump but may be related to patient behaviors and insulin dosing decisions. Before reaching the market, insulin pumps must obtain FDA approval and undergo rigorous testing by manufacturers to meet required standards such as the International Electrotechnical Commission 60601-2-24.

The OmniPod Insulin Management System (Insulet, Bedford, MA) is currently an integral part of the Artificial Pancreas Project sponsored by the Juvenile Diabetes Research Foundation. The artificial pancreas system (APS) is a system for automating closed-loop glucose control, comprising a glucose sensor, a controller/algorithm, human user interface, and an insulin pump.[4] During discussions for an investigational device exemption and master file (FDA MAF #1625) submission of the APS, we received a request from the FDA to reconfirm the dose accuracy of the FDA-approved OmniPod as an integral part of the APS. They wanted our group to demonstrate that the pump was accurate at its lowest dosing increment. The control algorithm of the APS calculates the amount of insulin to be delivered based on frequent glucose input data from a continuous glucose sensor. Assuring the accuracy of the pump is an integral step in the validation process. The FDA believed there was a need for additional bench test data to support the accuracy of the OmniPod at the smallest delivery volume.

To address this concern, we implemented method 1 (discussed later), to measure the accuracy of the OmniPod using a standard graduated pipette. After submitting the results, the FDA requested additional bench testing. We were also asked to provide justification of the fact that the measuring error is independent of the insulin amount to be measured. To answer these concerns, we implemented method 2 and provided theoretical statistical explanations (discussed later).

Interestingly, *in silico* research by Chan and colleagues[5] has shown that random pump errors with standard deviations (SDs) up to 10% of the expected pump output do not cause significant plasma insulin variability with pulsatile injections. This finding requires additional *in vivo* verification for clinical and further research significance.

Methods

We implemented two new approaches for assessing pump accuracy. A total of seven OmniPod insulin pumps were tested at bolus doses of 0.05, 0.1, 0.2, 1, and 6 U. Additional materials included a digital microscope (Dino-Light, running software DinoXcope v1.1) and a standard 100 µl pipette (equivalent to a 10 U volume of insulin). Using these simple tools, we were able to calculate the delivered volumes and its variability. Each method had its own strengths and weaknesses. Method 1, for example, was better suited for measuring insulin doses above 0.2 U

because of the size of the pipette. Although, using standard statistical techniques,[6] method 1 could be used to look at the accuracy and precision of smaller boluses. Method 2, as described later, will only work for the smallest bolus delivery volume but would be the best way to measure accuracy of these small volumes.

Method 1

Pipette

A standard pipette was used as a linear measure tool to assess the amount of insulin delivered by the pump. Insulin (Humalog, Lilly, Indianapolis, IN) was tinted red with a drop of food coloring (McCormick, Sparks, MD) to aid in visualization. Five OmniPods were used for this experiment. Pumps were filled with insulin according to the manufacturer's instructions. Once activated and ready to be used, the distal tip of the OmniPod's cannula was fitted into the end of the pipette (see **Figures 1–3**). We performed multiple runs of each OmniPod at each of the following doses: 0.05, 0.1, 0.2, 1.0, and 6 U. For the 0.05, 0.1, and 0.2 doses, we estimated accuracy over a series of delivered doses. The reasoning for this is that it is very difficult to precisely measure individual dose of 0.05 U using a pipette of this size. Attempts were made to use smaller pipettes, but we were unsuccessful because of the mismatch of the inner diameter of the pipette and the outer diameter of the cannula (see **Figure 4**,

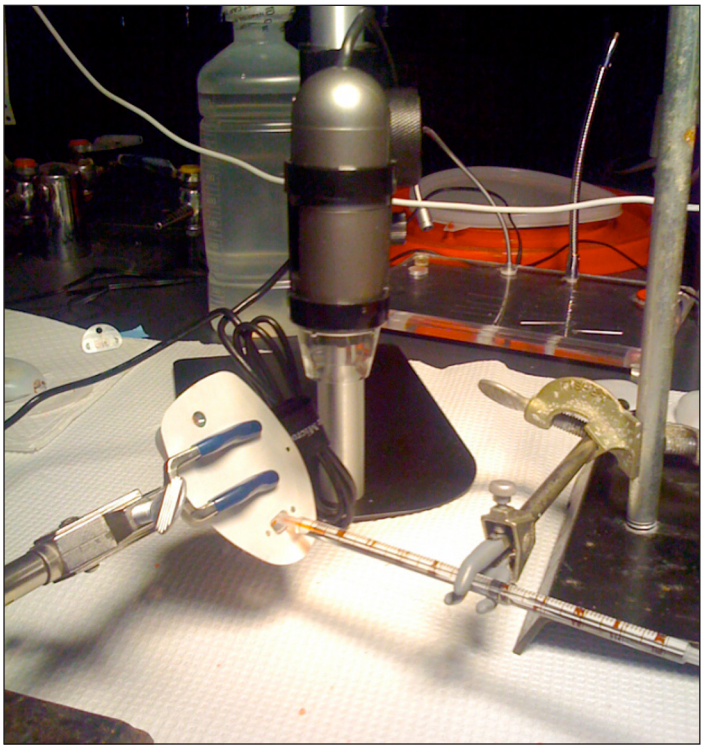

Figure 1. Distal tip of the OmniPod's cannula fitted into the pipette. The silver structure above the OmniPod is the digital microscope.

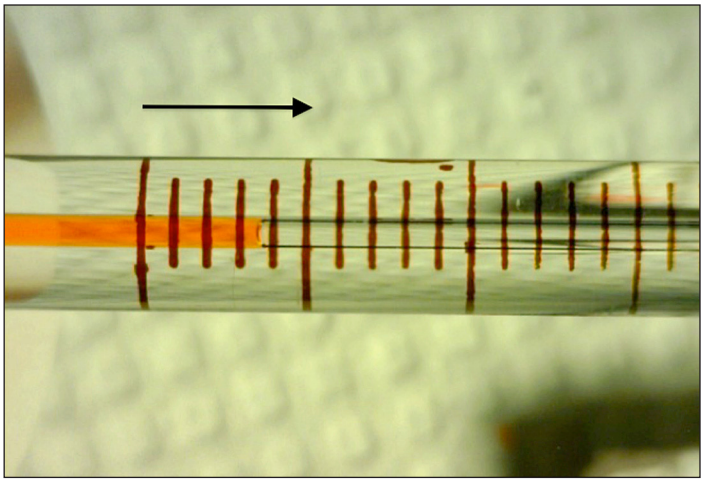

Figure 2. Standard pipette with labeling. The volume between small graduations is equal to 1 µl or 0.1 U, and the volume between the large graduations is equal to to 10 µl or 1 U.

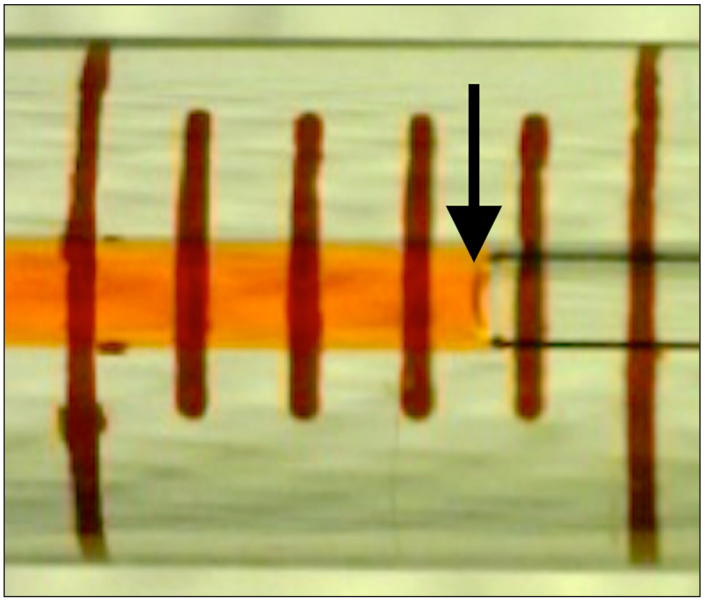

Figure 3. The arrow is pointing at the meniscus of the insulin level in the cannula.

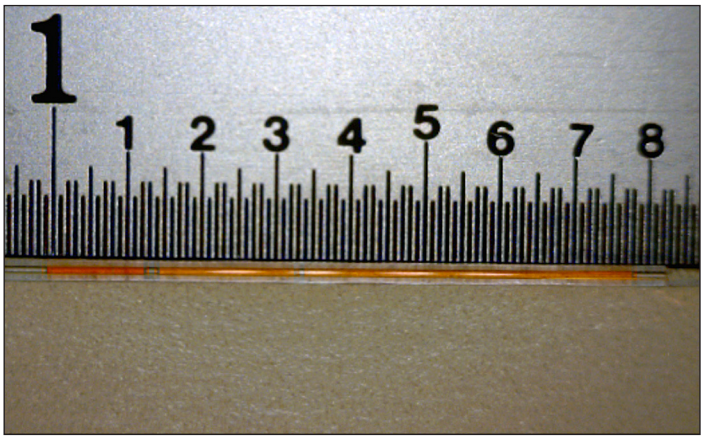

Figure 4. Attempts to use a pipette of smaller diameter creates a problem related to air bubbles.

which demonstrates air bubbles interfering with the accurate measurement when we attempted to use 0.5 and 1.0 μl pipettes). We estimated accuracy over 20 doses (0.05 × 20 = 1 U) and 10 doses for 0.1 and 0.2 U. Measuring 1 or 2 U provides less measuring error and thus is more accurate for estimation of the pump performance. The level of fluid in the pipette was measured to and from the meniscus level.

The cannula's graduations are too large to measure the volumes < 1 μl (0.1 U) accurately. Images from the microscope were additionally magnified to fit a 13" computer screen (MacBook, Apple, Cupertino, CA) using Adobe Reader software (v7.07). The volume level in the pipette was measured with a pixel precision using a standard metric ruler. Using a proportion with a known volume of 0.1 U (one small graduation), the given volume can be measured (see **Figures 1–5**).

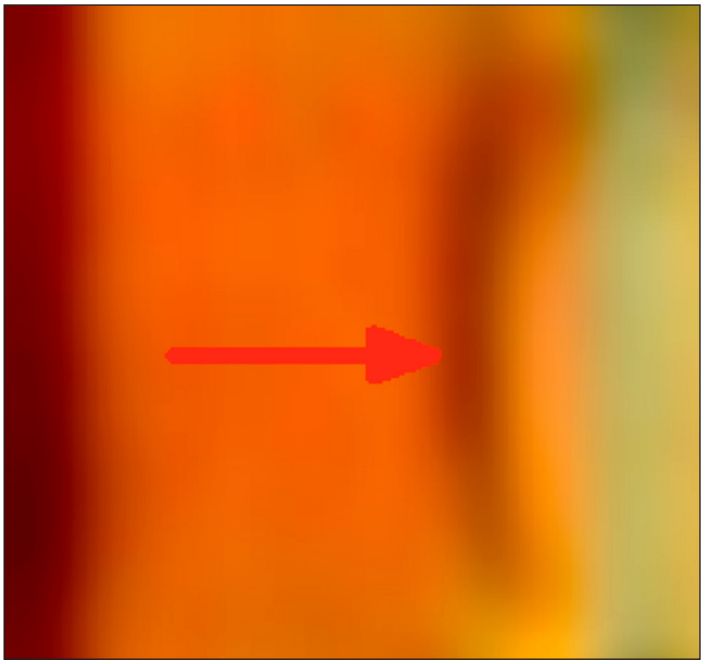

Figure 5. Magnified image of pipette with an arrow pointing at the meniscus.

Statistics

The challenge of measuring the accuracy of such small single insulin doses stems from the fact that the error of direct measurement is comparable to the measured quantities. The basic premise of the test methodology proposed here is that better estimates of single-dose properties can be obtained by considering the *sum* of multiple doses. The proposed solution is outlined as follows:

- When assessing pump accuracy, errors in insulin delivery (e.g., pump errors) must be distinguished from errors in the measurement of the delivered insulin (measurement errors).
- Assessment of errors in insulin delivery is of primary interest. Therefore, measurement methodology should be designed in a way that reduces the influence of measurement errors.
- In order to do so, we rely on classic techniques designed to use repeated measurements to reduce the uncertainty of measurement.

Thus we claim that repeated measurements of the sum of several single doses would yield a more precise estimate of the distribution of any *single dose* than the measurement of individual doses. Mathematical justification of this assertion is straightforward and is described in the **Appendix**. Intuitively, if we measure every single dose n times, we have n chances to make a measurement error. If we measure only the sum of several single doses, we have only one chance to make a measurement error of the same magnitude. Thus, when measuring every single pump pulse, we amplify the error in insulin delivery by the error of measurement. If we measure the sum of a sequence of single doses, then the error of measurement is negligible (relative to the amount of insulin delivered), which allows focusing exclusively on the error in insulin delivery.

As detailed in the **Appendix**, recovering single-dose characteristics from the combination of identically distributed doses is a commonly accepted technique using standard statistics based on assumption of independence of consecutive measurements—an assumption that is the basis for practically any statistical analysis. Most importantly, this is exactly the same assumption that would be used to estimate the SD of an individual dose if individual doses were measured. Thus there is no loss of generality in using a combination of doses compared with single doses.

In addition, as shown in the **Appendix**, the combined doses technique reduces the bias in estimation of the variance of delivered boluses in presence of measurement errors.

Results

At bolus dose of 0.05 U, mean delivered dose was 0.050 ± 0.003 U, 0.099 ± 0.005 U at 0.1 U, 0.2 ± <1e-5 U at 0.2 U, 1.001 ± 0.018 U at 1 U, and 6.03 ± 0.04 U at 6 U. The experiment environment was as follows: temperature

22.4–23.1 °C (72.4–73.6 °F) and barometric pressure 1015–1020 Pa (see **Table 1** and **Figures 6** and **7**).

Method 2

Spherical Bolus

We used a simple method of measurement using the microscope's field of view. If one knows the magnification power (150X in our case) along with a known measurement within the microscope's field of view [in this case, the outer diameter of the OmniPod's cannula (0.022 ± 0.0015 inches or 0.0558 ± 0.0038 cm)], then linear distances within the field can be measured (in this case, the diameter of the spherical bolus). **Figure 4** shows the distal tip of the cannula and the spherical insulin bolus. From the diameter, one can derive the radius and thus the volume of the bolus using the following formula:

$$V = \frac{4\pi r^3}{3} \quad (1)$$

Two OmniPods were used in this experiment. The OmniPods were filled with Humalog insulin (Lilly) per the manufacturer's recommendations. Insulin was tinted with food coloring, just as in the previous method. Each Omni-Pod delivered 20 individual boluses of 0.05 U (0.5 µl). Using this method, we could actually measure the volume of each 0.05 U bolus as opposed to method 1, in which we needed to average the error after summing multiple boluses (see **Figure 8**).

Results

The first OmniPod delivered an average bolus of 0.504 ± 0.013 µl (mean total diameter = 0.9879 mm). The second OmniPod delivered an average bolus of 0.506 ± 0.015 µl. All results fall into the previously estimated 95% confidence interval. The experiment environment was as follows: temperature 22.2–22.7 °C (72–73 °F) and barometric pressure 1014–1016 Pa (see **Table 2**).

We have also compared the two methods by comparing the results for delivering 0.5 µl of insulin by the OmniPod (see **Figure 9**). Difference was found to be not statistically significant, $p = .86$.

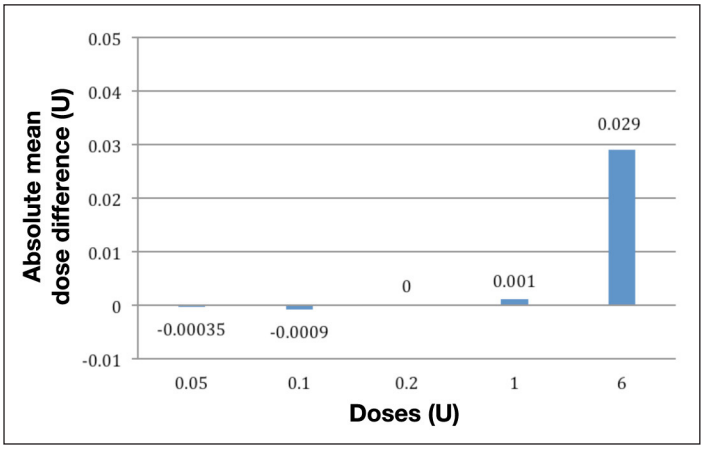

Figure 6. Absolute mean deviation from the target dose.

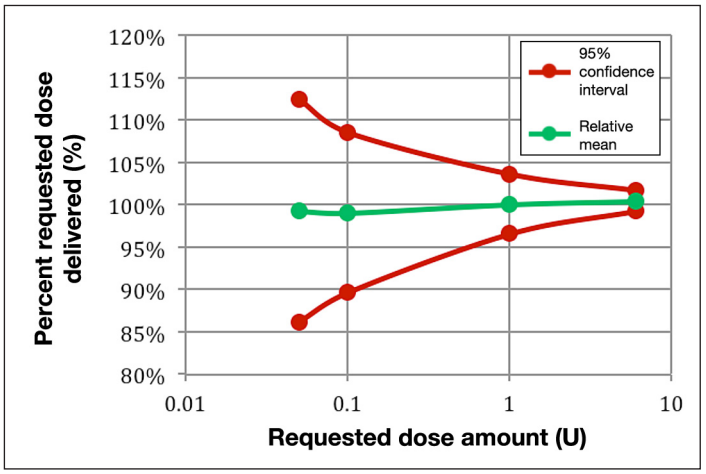

Figure 7. Trumpet curve showing relative mean percent accuracy for doses delivered. Red line represents 95% confidence interval; logarithmic scale is used.

Table 1.
Results of Method 1 Showing Mean Dose Delivered across All Tested Bolus Doses as well as Standard Deviation, 95% Confidence Interval, Relative Error, and Relative Standard Deviation

Bolus dose (U)	Repetitions	Mean bolus dose (U)	SD (U)	95 confidence interval (U)	Relative error	Relative SD
0.05	20	0.050	0.003	0.043–0.056	-0.7%	6.7%
0.1	10	0.099	0.005	0.090–0.109	-0.9%	4.8%
0.2	5	0.2	0	0.2–0.2	0.0%	0.0%
1	10	1.001	0.018	0.966–1.036	0.1%	1.8%
6	10	6.029	0.037	5.957–6.101	0.5%	0.6%

Discussion

Insulin is often given in small doses (<1 U), especially to children and infants with type 1 diabetes. Dosing is weight adjusted, and precision is paramount. Overdosing insulin can cause life-threatening hypoglycemia, early symptoms of which small children or infants may not be able to identify or show. Underdelivering insulin is potentially dangerous due to development of acute DKA and long-term complications, such as cardiovascular disease, retinopathy, nephropathy, neuropathy.[7] Both extremes of hypoglycemia or hyperglycemia may lead to coma or death.

Insulin is currently administered via syringes, pens, or pumps. Several studies have assessed the accuracy of syringes and pens delivering low doses of insulin.[8–11] A study by Keith and associates[8] compared accuracy of two syringes, three pens, and one pump. Syringes were found unacceptably inaccurate at doses lower than 5 U, overdosing by as much as 31% at a 1 U dose.

At the dose of 5 U, all devices were reasonably precise and accurate (<5% error for all devices), which was not true for smaller doses of 1 and 2 U. Pump (H-TRON-plus V100, Disetronic Medical Systems Inc.) was the most precise device, with tendency to underdose. None of the devices were both precise and accurate at doses less than 5 U. In this review, we compared data from Keith and associates[8] to OmniPod data acquired by method 1, looking at the accuracy of different devices delivering 1 U of insulin. Other studies by Casella and coworkers,[9] Gnanalingham and colleagues,[10] and Lteif and Schwenk[11] produced similar results, concluding that syringes are very inaccurate and pens are more accurate than syringes at delivering small doses of insulin (<5 U). Another observation related to insulin pens noted during this project was that, if the plunger end of a pen was depressed after the dose had been administered, additional insulin was expressed from the needle tip. This amount was not quantified.

Continuous subcutaneous insulin infusion via pumps provides fewer fluctuations in insulin–glucose profile

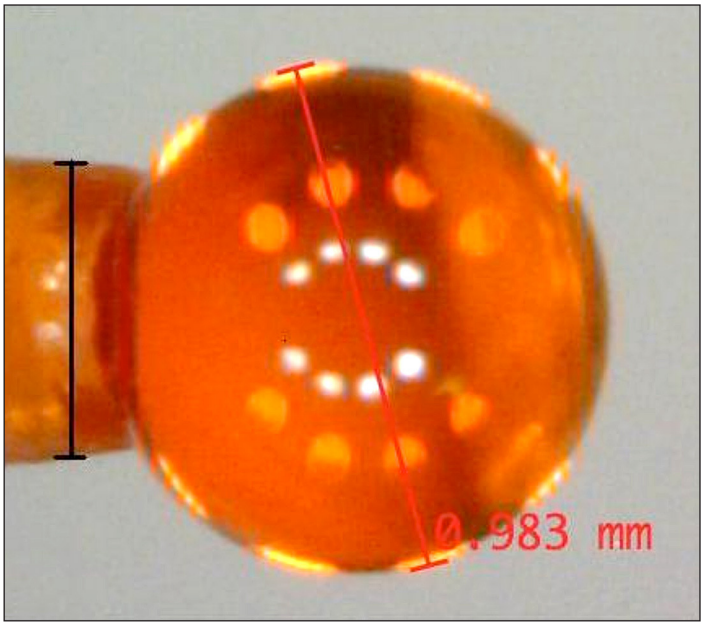

Figure 8. Distal tip of the cannula and a spherical insulin bolus. The outer diameter of the OmniPod's cannula (black bar) measures 0.022 ± 0.0015 in. or 0.0558 ± 0.0038 cm.

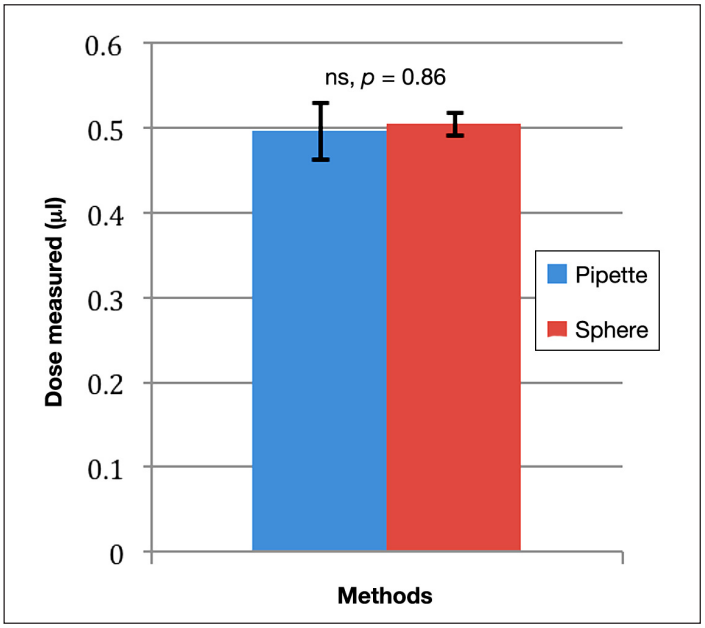

Figure 9. Pipette versus sphere for an OmniPod delivering 0.5 µl of insulin. ns, not significant.

Table 2.
Results of Method 2 Showing OmniPod 1 and OmniPod 2 Delivering Target 0.5 µl of Insulin

	Target dose (µl)	Runs, (*n*)	Mean measured diameter (mm)	Mean delivered dose (µl)	SD	95 confidence interval	*Z* score
OmniPod 1	0.5	20	0.98735	0.504	0.013	0.00569739	.689
OmniPod 2	0.5	20	0.98845	0.506	0.015	0.00657391	.689

and has been shown to improve patient glycemic control and lower insulin dose requirements.[12–18]

There are limited data on insulin pump dosing precision, but several studies have shown that there are limitations in traditional pump design, which may adversely affect the treatment. The study by Zisser and associates[19] showed a siphon effect of conventional insulin pumps. In the benchtop study, changes in insulin delivery depend on the position of the cannula, ranging from 74.5% of expected dose when pumping upward to 123.3% when pumping downward at a rate of 1 U/h. Insulin delivery of the OmniPod system was not affected by pumping direction.

Two new approaches were applied to measure the volume delivery of the OmniPod insulin pump. Both methods require simple tools, are fast, and show good reproducibility. Method 1 showed OmniPod's high accuracy (>99%) and precision (93.3% to 99.4%), and method 2 confirmed these results at the lowest delivery volume, with all results falling into the 95% confidence interval estimated by method 1. In addition, there was no statistical difference between the results of method 1 and method 2 (*t*-test $p = .86$). Both methods can be applied for measuring volume delivery of other types of medical pumps as well.

In the future, visualization methods for quantifying amounts of insulin could be further optimized using image analysis software. For method 2, image analysis tools could be used to measure multiple diameters of the sphere and derive a measurement with a higher degree of accuracy.

Conclusion

Bench testing results obtained during two experiments showed that OmniPod is extremely accurate, with a relative error ranging from -0.9% to 0.96% for all doses (0.05, 0.1, 0.2, 1, and 6 U). This is much lower than any other insulin injection devices previously tested by Keith and associates[8] (see **Figure 10**), Gnanalingham and colleagues,[10] and Lteif and Schwenk.[11]

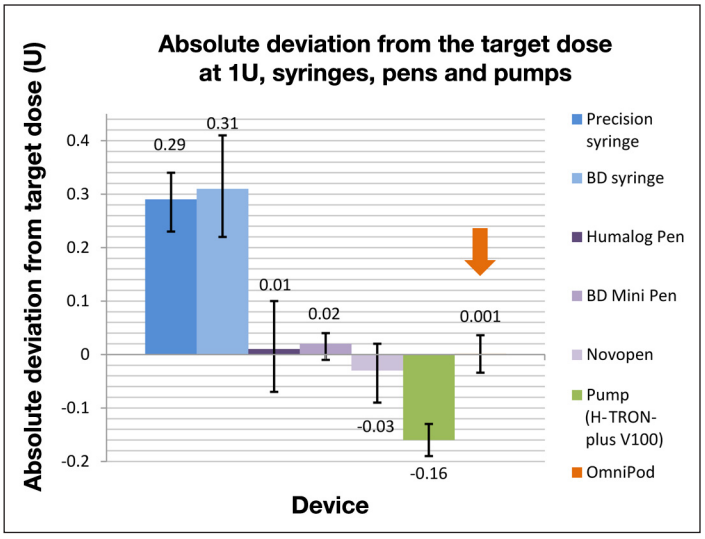

Figure 10. Absolute deviation from target dose at 1 U for syringes, pens, and pumps.

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Disclosures:

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References:

1. U.S. Food and Drug Administration; Center for Devices and Radiological Health. White paper: infusion pump improvement initiative. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/ucm205424.htm.
2. IData Research. U.S. market for diabetes monitoring, treatment and drug delivery 2010.
3. Cope JU, Morrison AE, Samuels-Reid J. Adolescent use of insulin and patient-controlled analgesia pump technology: a 10-year Food and Drug Administration retrospective study of adverse events. Pediatrics. 2008; 121(5):e1133-8.
4. Dassau E, Zisser H, C Palerm C, A Buckingham B, Jovanovič L, J Doyle F 3rd. Modular artificial beta-cell system: a prototype for clinical research. J Diabetes Sci Technol. 2008; 2(5):863-72.
5. Chan A, Breton MD, Kovatchev BP. Effects of pulsatile subcutaneous injections of insulin lispro on plasma insulin concentration levels. J Diabetes Sci Technol. 2008;2(5):844-52.
6. Scheaffer RL. Introduction to probability and its applications. 2nd ed. Belmont: Duxbury; 1995.
7. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329(14):977-86.

8. 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.
9. Casella SJ, Mongilio MK, Plotnick LP, Hesterberg MP, Long CA. Accuracy and precision of low-dose insulin administration. Pediatrics. 1993;91(6):1155-7.
10. 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.
11. Lteif AN, Schwenk WF. Accuracy of pen injectors versus insulin syringes in children with type 1 diabetes. Diabetes Care. 1999;22(1):137-40.
12. Edelman SV, Bode BW, Bailey TS, Kipnes MS, Brunelle R, Chen X, Frias JP. Insulin pump therapy in patients with type 2 diabetes safely improved glycemic control using a simple insulin dosing regimen. Diabetes Technol Ther. 2010;12(8):627-33.
13. Wolff-McDonagh P, Kaufmann J, Foreman S, Wisotsky S, Wisotsky JA, Wexler C. Using insulin pump therapy in poorly controlled type 2 diabetes. Diabetes Educ. 2010;36(4):657-65.
14. Gentry CK, Cross LB, Gross BN, McFarland MS, Bestermann WH. Retrospective analysis and patient satisfaction assessment of insulin pump therapy in patients with type 2 diabetes. South Med J. 2011;104(1):24-8.
15. Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M. Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. Pediatrics. 2006;117(6):2126-31.
16. Hanaire-Broutin H, Melki V, Bessières-Lacombe S, Tauber JP; Study Group for the Development of Pump Therapy in Diabetes. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. Diabetes Care. 2000;23(9):1232-5.
17. Hirsch IB, Bode BW, Garg S, Lane WS, Sussman A, Hu P, Santiago OM, Kolaczynski JW; Insulin Aspart CSII/MDI Comparison Study Group. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. Diabetes Care. 2005;28(3):533-8.
18. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. Diabetes Care. 2003;26(4):1079-87.
19. Zisser HC, Bevier W, Dassau E, Jovanovic L. Siphon effects on continuous subcutaneous insulin infusion pump delivery performance. J Diabetes Sci Technol. 2010;4(1):98-103.

Appendix: Mathematical Justification of the Method for Reducing the Influence of Measurement Errors in the Analysis of Accuracy of Insulin Pumps Delivering Small Amounts of Insulin

In order to design the experiment and analyze data in a way that reduces measurement errors, we use the following methodology:

Step 1. Perform a set of k experiments, each experiment consisting of a series of n single doses to be delivered by the insulin pump. Denote each single dose obtained at experiment j by $\xi_{1j}, \xi_{2j}, \ldots, \xi_{nj}$, $j=1,2,\ldots, k$, and let each ξ_{1j} have a certain mean μ and SD σ.

Step 2. After each experiment, measure only the sum of all single doses delivered, i.e., cumulative amounts, but not the insulin delivered at each single dose. This results in observations on the cumulative amount $\eta_1, \eta_2, \ldots, \eta_k$ —one per experiment defined as

$$\eta_1 = \xi_{11} + \xi_{21} + \ldots + \xi_{n1}$$

$$\eta_2 = \xi_{12} + \xi_{22} + \ldots + \xi_{n2}$$

$$\ldots\ldots\ldots\ldots\ldots$$

$$\eta_k = \xi_{1k} + \xi_{2k} + \ldots + \xi_{nk}$$

Step 3. Estimate the mean and the SD of the cumulative amount η, e.g., $[E\eta, SD(\eta)]$, using standard mean/SD formulas valid under broad statistical assumptions:

$$E\eta = \frac{1}{k}\sum_{j=1}^{k}\eta_j \text{ and } SD(\eta) = \sqrt{\frac{1}{k-1}\sum_{j=1}^{k}(\eta_j - E\eta)^2}\,.$$

Step 4. From estimates of the mean and the SD for the cumulative amounts, derive estimates for mean and SD of a single dose ξ of insulin delivered by the pump:

$$\mu = \frac{1}{\eta}E\eta \text{ and } \delta = \frac{1}{\sqrt{\eta}}SD(\eta).$$

The only difference between this test methodology and direct measurement of individual doses is that here we measure cumulative amounts instead of single doses and then process the data using steps 3 and 4. All statistical assumptions are identical between the two methods and include

(i) the variations in the delivered doses are (for a constant desired amount) random and independent and

(ii) the measurement errors for individual doses are independent.

In both cases, the final result is estimation of the mean and SD for a single dose delivered by the pump. For example, if the goal is to estimate the error of delivery of 0.05 insulin units, we perform $k = 10$ experiments, each requesting a series of $n = 20$ single doses of 0.05 U to be delivered (i.e., each experiment delivering approximately 1 U of insulin). Then only the sum of each series is measured, which gives us $k = 10$ measurements of the cumulative mean. From these $k = 10$ measurements, steps 3 and 4 are used to derive the mean and the SD for a single 0.05 U dose.

Further, denote the measurement error by δ. A series of k measurement errors will then be represented by random variables $\delta_1, \delta_2, \ldots, \delta_k$ that have certain mean m (typically zero) and certain SDs. Because the error of measurement is independent from the error of insulin delivery and is independent from the amount of insulin to be measured, the same-magnitude error δ will be present when measuring individual doses or a cumulative dose. Now, consider two measurement scenarios and note that each of the two scenarios requires exactly k measurements, i.e., the demands are identical:

Scenario 1: Small insulin amounts (e.g., 0.05 U) are requested, and each amount is measured individually to assess the pump error of single-dose insulin delivery, yielding a series of observed insulin amounts: $\xi_1 + \delta_1, \xi_2 + \delta_2, \ldots, \xi_k + \delta_k$ (because the error of measurement δ is present when measuring every single insulin dose). The mean of the delivered insulin is then estimated using the following formulas:

$$\mu = \frac{1}{k}\sum_{j=1}^{k}(\xi_j + \delta_j) = \frac{1}{k}\sum_{j=1}^{k}\xi_j + \frac{1}{k}\sum_{j=1}^{k}\delta_j.$$

Thus the expected value of the mean will be $E\mu = \mu + m$, where m is the mean of the measurement error δ as defined earlier.

Scenario 2: Small insulin amounts (e.g., 0.05 U) are requested from the pump in k series of n single doses each, and only the cumulative amounts $\eta_1, \eta_2, \ldots, \eta_k$ are measured. With measurement error δ, the cumulative amount measured will be $\eta_1 + \delta_1, \eta_2 + \delta_2, \ldots, \eta_k + \delta_k$. The mean insulin delivered in each single dose ξ is then derived from the estimates of η, as follows:

$$\mu = \frac{1}{n}\left(\frac{1}{k}\sum_{j=1}^{k}(\eta_j + \delta_j)\right) = \frac{1}{nk}\sum_{i=1}^{k}\left(\left(\sum_{i=1}^{n}\xi_{i,j}\right) + \delta_j\right).$$

Thus the expected value of the mean would be

$$E\mu = E\left[\frac{1}{nk}\sum_{j=1}^{k}\left(\left(\sum_{i=1}^{n}\xi_{i,j}\right) + \delta_j\right)\right] = E\mu = \frac{1}{\pi k}\sum_{j=1}^{k}\sum_{i=1}^{n}E[\xi_{i,j}] + \frac{1}{\pi k}\sum_{j=1}^{k}E[\delta_j] = \mu + \frac{m}{n}$$

Comparing scenarios 1 and 2, we see that the influence of the measurement bias is reduced n-fold when only the cumulative amount η is measured, as compared with measuring each single dose individually. Similarly, the variance of a single-dose measurement estimated under scenario 1 would be biased by s^2, while the variance of a single-dose measurement under scenario 2 would be biased by s^2/n.[6]

In conclusion, scenario 2 reduces the influence of the error of measurement by a factor of n (the number of single doses added within a cumulative measurement) and should be the preferred test methodology when the error of individual measurement is comparable to the amount of insulin to be measured. This is particularly relevant to small single doses, i.e., 0.2 U or below.