Smart Insulin Pens
Addressing the Unmet Needs of Healthcare Professionals and Patients


MDI Patient Clinical Needs

Missing 2 Doses per week can lead to an increase in A1C of up to 0.4%.1

2/3 of people need help calculating their insulin doses.2-4

60% of insulin doses are taken with some insulin-on-board.2-4

Lack of accurate dosing data creates a significant barrier to optimizing glycemic control.5

Available FDA Approved Insulin Delivery Devices

Convenience
Smart Insulin pens provide the patient access to smart dosing support in a non-wearable format.

Cost
Smart Insulin Pens are covered as a pharmacy benefit with a small copay.

Complexity
Smart Insulin Pens address numeracy limitations by providing smart dosing support through a pen paired to an integrated app.

Roadmap criteria for Smart Insulin Pens

<table>
<thead>
<tr>
<th>Legacy Delivery</th>
<th>Tracking Insulin Pen (TIP)</th>
<th>Smart Insulin Pen (SIP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE 0</td>
<td>STAGE 1</td>
<td>STAGE 2</td>
</tr>
<tr>
<td>Vials / Syringes</td>
<td>Tracking Insulin Pen</td>
<td>Real-Time Tracking Insulin Pen</td>
</tr>
<tr>
<td>Traditional Insulin Pen</td>
<td>Retrospective, prescriptive dose data</td>
<td>Real-time data with BBS and reminders with cloud connectivity</td>
</tr>
</tbody>
</table>

Critical Criteria must be met in order to proceed to stages 4 and 5 of SIP categories.

Less complexity
Automatically records dose and time of insulin administration, reminds if dose is not taken within a scheduled time frame, ability to differentiate prime and bolus doses, provides insulin dose recommendation based on personalized settings (ISF, ICR, Target BG, DIA), and accurate insulin-on-board (IOB).

Integrated data
Integrates with other devices and data technologies such as CGM and Bluetooth blood glucose meters, ability to share integrated data reports with the care team.

Convenience
No need to wear an additional device, continuous use for at least one year (durable; 1 year battery), automatically responds to changes in time zones.

The first and only Smart Insulin Pen system paired to an integrated diabetes management app.

InPen™ combines an innovative diabetes management app with a Bluetooth® wireless technology insulin pen. The easy-to-use app simplifies the constant recording, monitoring, and calculating required for successful multiple daily insulin injection therapy.

InPen Meets all Critical Criteria for a Smart Insulin Pen

✅ FDA cleared and commercially available
✅ Syncs with smartphone
✅ Clinical decision support with automated insulin dose calculator
✅ Dose, BG, temperature and insulin expiration alerts, and notifications
✅ Integrates with other devices and data
✅ Ability to directly share integrated data with the care team
✅ Auto responds to changes in time zones
✅ 1-year durable battery

Discover the features of InPen

Smart Dosing based on Smart Settings
Automatically records insulin doses and recommends doses based on current blood glucose, carb intake and accurate tracked insulin-on-board (IOB).

Smart Reminders
Missed dose reminders for mealtime and basal insulin doses, blood glucose check - keeping patients on track.

Smart Reporting
Data reports shared directly from the app include time and amount of insulin doses integrated with glucose and carbohydrate intake data giving the complete picture of daily diabetes care.

To learn more visit www.CompanionMedical.com or call 844.843.7903.

RX Only. The Bluetooth® Wordmark and logos are owned by Bluetooth® SIG, Inc. Other trademarks and trade names are those of their respective owners. InPen logo is a trademark of Companion Medical. Copyright © 2019 Companion Medical and/or its affiliates. All rights reserved. LBL-00559-AA
Smart Insulin Pens Will Address Critical Unmet Needs for People with Diabetes Using Insulin

David Kerr, MBChB DM FRCP FRCPE*, MD, Hope Warshaw, MMSc, RD, CDE, BC-ADM+, Nicholas Y Choi, BS*
*Sanoma Diabetes Research Institute, 2219 Bath Street, Santa Barbara, CA 93105
+Hope Warshaw Associates, LLC, 70 Blackwood Road, Asheville, NC 28804

INTRODUCTION

The use of insulin to manage either type 1 (T1D) or type 2 diabetes (T2D) is neither easy nor straightforward. For the 7.4 million Americans (Cowie CC, et al. 2017) using insulin on a daily basis and for individuals starting insulin, personal objectives and circumstances, clinician recommendation, and health plan coverage contribute to the choice of insulin delivery device. Traditionally, insulin has been given as an injection using a syringe or pen, or as a continuous subcutaneous insulin infusion (CSII) with a pump or patch, or more recently, as a fast-acting inhaled insulin by a small number of individuals. Worldwide, traditional pens are the most widely used devices for delivering insulin [Bailey and Scott, 2017; Grif et al., 2019].

People who choose not to use CSII do so for various reasons, including lack of desire to wear a device continuously, the burdensome requirement to master potentially complex technology, device insertion and changes and maintaining an inventory of related supplies. Although CSII can provide clinical and lifestyle benefits in T1D, this form of insulin delivery may be less cost-effective than multiple daily injections of insulin (MDI). Also, CSII is used less often in minority populations with T1D compared with non-Hispanic whites [Foster et al., 2019; Gill, et al. 2019]. In T2D, uptake of CSII continues to be very low.

CURRENT CHALLENGES FOR INSULIN USERS AND CLINICIANS

Taking daily insulin is complex and challenging (Table 1). Clinicians also face challenges in helping people with diabetes maximize their potential benefits from a prescribed regimen due to the lack of objective data on the dose and timing of insulin administration for those using injections. To date, this assessment must be done through self-reports, logbooks and other recording tools shared by the person with diabetes. Extracting, reviewing and analyzing this data for clinical decision-making is time consuming and fraught with inaccuracies. Yet, over time this has been the data with which clinicians have had to make clinical decisions on insulin dosing. Despite the considerable need, there are no national or international clinical practice guidelines that explicitly recommend that insulin users log information about their insulin doses and timing. The absence of this data may compound the day-to-day challenges faced by MDI users (Table 1).

Unlike insulin pump users, people who use legacy insulin dosing devices, such as syringes or disposable pens, must make important daily decisions to administer insulin without access to reliable information on previous doses given, the residual insulin still active (insulin-on-board) and other confounding variables (e.g., exercise, travel across time zones and changes in insulin sensitivity). Specifically, there is the daily burden of remembering to take insulin.

Recent data from MDI-treated individuals using continuous glucose monitoring devices (CGM) suggested that one in four meals are associated with either a late or missed insulin bolus [Norlander et al., 2018]. Insulin omission occurs in older as well as younger individuals and in T2D as well as T1D. In a study using a Bluetooth-enabled insulin pen cap [Munshi et al., 2019], insulin omission occurred in 100 percent of participants over a one-month period. The impact of a missed insulin dose can be significant. For example, forgetting two meal-related doses each week is associated with a 0.3-0.4% increase in HbA1c levels and missing basal injections can lead to a 0.2-0.3% change [Randlov and Poulsen, 2008].

Insulin omission can occur for a number of reasons including simple forgetfulness, embarrassment, dose complexity, and financial cost. Omission can also be deliberate as in the case of eating disorders. Another factor affecting the complexity of doses insulin is numeracy skills. Calculating a safe and effective dose of insulin requires numeracy skills. Limited numeracy skills have been shown to influence achieved HbA1c levels [Marden S, et al. 2012]. Therefore, the ability for MDI users to automatically upload and analyze insulin dosing information has the potential to: (a) reduce the personal burden of insulin self-management; (b) improve the safety of insulin therapy; and (c) allow clinicians greater opportunities to work with insulin users to achieve clinical and personal goals through optimization of insulin therapy.

THE EVOLUTION OF SMART INSULIN PENS (SIPs)

To support safe and effective MDI therapy, a number of devices have been developed with features of potential value for insulin users such as bolus calculators, digital log books with retrospective dose data, and dose reminders and alerts. The clinical trial conducted by Ziegler et al. on bolus calculator/advisors integrated with a blood glucose

Table 1. Challenges of Implementing and Managing an Insulin Regimen

<table>
<thead>
<tr>
<th>Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recording doses and times</td>
</tr>
<tr>
<td>Managing and analyzing data to adjust doses to achieve glycemic goals</td>
</tr>
<tr>
<td>Fears and concerns about hypoglycemia</td>
</tr>
<tr>
<td>Numeracy skills to calculate doses</td>
</tr>
<tr>
<td>Missed, delayed or incorrectly timed doses</td>
</tr>
<tr>
<td>Inability to determine if and when doses were taken</td>
</tr>
<tr>
<td>Inability to easily determine insulin-on-board</td>
</tr>
<tr>
<td>Potential for insulin stacking (overlap of bolus doses)</td>
</tr>
</tbody>
</table>

Table 2. Nine Critical Functions that Meet the Criteria for Smart Insulin Pens

1. No need to wear or carry an additional device beyond a smartphone
2. Provides continuous use for at least one year
3. Automatically responds to changes in a user’s time zone
4. Automatically records and tracks the dose and timing of insulin administration with the option of sharing this information with a clinical team
5. Reminds if insulin dose not taken within a customized scheduled time frame
6. Ability to differentiate priming dose from a bolus dose. This is especially required to ensure accurate tracking of insulin-on-board estimations.
7. Provides access to clinical decision support with personalized settings. These settings should include carbohydrate-to-insulin ratios, glucose level correction factors (also referred to as Insulin Sensitivity Factor) and tracking insulin on board information (also referred to as Duration of Insulin Action) from prior bolus insulin doses for more precise insulin dosing and reducing the risk for hypoglycemia
8. Ability to integrate with other diabetes technologies (e.g. continuous glucose monitoring), wearables (e.g. activity monitors) and digital therapeutic platforms
9. Allows a person with diabetes and team to communicate virtually allowing remote monitoring as a service
meter showed improvements in HbA1c levels and greater treatment satisfaction without increasing hypoglycemia risk in people using MDI.

To date, clinicians have offered these technologies to individuals with diabetes based on one or more of the following situations: (a) changes in therapy (e.g., insulin initiation); (b) perceived failures of existing approaches (e.g., rising HbA1c levels or recurrent hypoglycemia); (c) clinical factors (e.g., planning pregnancy); (d) cost (e.g., insurance coverage and personal time burden); (e) a priori perceptions of benefits (e.g., consumerism); (f) human factors (e.g., ability to use the technologies); (g) psychosocial influences (e.g., social determinants of health); (h) as well as on the experience and enthusiasm of the prescribers themselves.

Currently, several insulin delivery devices such as pens, caps and clips that go on or attach to an insulin pen, are either on the market or in development. These devices cater to people who use MDI and address the numerous challenges addressed in Table 1. However, most of these devices do not have key functions integrated into the technology that meet the criteria detailed in Table 2 that defines Smart Insulin Pens (SIPs).

Several years ago Kowalski proposed a roadmap for the development of artificial pancreas systems [Kowalski, 2015]. In Figure 1, we propose a conceptually similar roadmap for the development and evolution of SIP systems. A significant benefit of a SIP is that the intelligence and interface of the technology is located in the user’s smart phone, an item most people carry as part of their everyday life. In 2018, according to Pew Research, the penetration of smartphone ownership is 92% of millennials (25 – 37 years of age), 85% of GenXers (38 – 53 years of age), 67% of Baby Boomers (54 to 72 years of age) and 50% of the Silent Generation (73-90 years of age). Another benefit of a SIP is that the user will have access to many of the capabilities of CSII but without the need to wear or carry the associated hardware. Having access to automatically collected data using a SIP is likely advantageous in a number of clinical settings especially when combined with "smart intelligence" [Klonoff and Kerr, 2018].

The first FDA-cleared SIP, the InPen™ System, was launched in 2017 [Bailey and Stone, 2017]. To date, this is the only SIP that meets the Stage 4 criteria described in Figure 1 and has obtained both FDA-clearence (510(k)) in the US and CE mark for the European Economic Area. This device records the amount and timing of each insulin dose and wirelessly transmits the information via Bluetooth to a proprietary mobile smartphone application (app.) The associated app also tracks insulin-on-board, makes dosing recommendations, and offers other clinical decision support. The app prepares and sends reports to clinicians in an integrated format similar to a CSII download. Figure 2 provides a graphic of available insulin delivery devices including InPen.

It is expected that other SIPs that meet the criteria outlined in Table 2 and as described in Figure 1, will enter the marketplace in the future. It can be envisioned that SIPs will become a core tool for insulin therapy with the ability to add additional features to support specific clinical scenarios such as long-haul travel across time zones, exercise, and insulin initiation in T2D.

An indirect benefit of SIPs will be the ability to use currently available and new Insulins including bio-similar and human insulin products. This will have the potential to allow underserved populations of people with diabetes to access intensive insulin therapy technologies more easily than at present. As with all technology-dependent devices, there are several challenges worth noting for SIPs coming to the market. These include cost and creating a user interface and experience (UI and UX) that will be “sticky” for sub-populations of people with diabetes (e.g. young versus older, new onset versus established diabetes and taking into consideration the specific needs of racial and ethnic groups). Therapeutic inertia, the lack of knowledge about and/or unwillingness to discuss or prescribe novel tools, can play a role for both clinicians and people with diabetes [American Diabetes Association, 2018]. To minimize this particular challenge, it is important that the broad spectrum of clinicians caring for people with diabetes who use insulin become aware of SIP and able to discuss their potential availability and advantages.

A GLIMPSE INTO OUR CONNECTED FUTURE

In the not too distant future, clinicians and people with diabetes will work within a “Digital Diabetes Ecosystem” [Kerr et al., 2018]. This will combine the Internet of Medical Things (connected physiological and behavioral sensors embedded within multiple medical devices worn or used by an individual) and a SIP. We expect that insulin dosing data will be augmented with artificial intelligence and machine learning to predict and prevent adverse events such as hypoglycemia and make more effective dose calculations. A positive result will be the replacement of current insulin dosing devices with SIP and a combination of sensors, transmitters, and the capability to integrate with other diabetes data collection systems.

Overall, mobile/smartphone applications capable of integrating with Bluetooth-enabled diabetes devices will continue to improve and simplify diabetes management for all involved. These technologies will enable expanded use of telemedicine, virtually delivered care and remote patient monitoring. By harnessing the potential of technology to identify patterns from insulin dose data for the purpose of insulin decision support, we are at last on the verge of reducing the tremendous day-to-day burden faced by millions of people living with diabetes.

Disclosures: David Kerr is an advisor to Globalm, HIHealth, and Vicentra, and has provided consultancy and/or advisory board services to Abbott Diabetes Care, Ascensia, NovoNordisk, Sanofi and Companion Medical. He is in receipt of research support from Lilly and NovoNordisk. Hope Warshaw has served as a consultant to Concom Sensing. Both authors have been compensated by Companion Medical for their time in authoring this paper.

References:
Gripp ET. Diabetes Care 2019:e2455–522. doi:https://doi.org/10.2337/dc18-185