Performance of a Continuous Subcutaneous Insulin Infusion (CSII) Pump With Acoustic Volume and Flow Sensing in Simulated High-Consequence Situations

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Abstract*—*Goal: **An insulin pump's failure to deliver insulin in the right amount at the right time is a preventable cause of hospitalization. We evaluated key performance metrics of a novel insulin pump that prevents "silent insulin non-delivery" caused by blockage, delivery of air and site leakage. This is accomplished via an acoustic sensor that measures the volume of insulin delivered with each pulse in real-time. *Methods:* We tested long and short-term flow accuracy, occlusion-detection time and pressure, and air management of the new device (ND) versus 3 U.S. commercial insulin pumps (CIPs) using standardized methods. *Results:* The ND outperformed CIPs on long-term basal flow rate error. Occlusion detection was 5 to 22.5 times faster depending on the basal rate and resulted in significantly lower (2 to 5x) pressures at time of occlusion. With air included in the drug reservoir, the tested CIPs can infuse air without detection, while the ND prevented air delivery without interruption. *Conclusions:* Bench tests of the ND versus 3 commercially available pumps showed improved occlusion detection and air management without flow performance tradeoffs. Additionally, the lower delivery pressure measured at time of occlusion suggests a substantially lower potential for site leakage at both basal and bolus rates. These enhancements combine to decrease the likelihood of silent insulin non-delivery.**

***Index Terms*—CSII (continuous subcutaneous insulin infusion), DKA (diabetic ketoacidosis), insulin pump malfunction, metrology for drug delivery, occlusion detection.**

***Impact Statement*—A novel continuous subcutaneous insulin infusion pump demonstrated improved detection of silent occlusions and reduced potential for air delivery and site leakage versus a set of 3 commercially available pumps, which may improve Type-1 diabetes management.**

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I. Introduction

CONTINUOUS subcutaneous insulin infusion (CSII) pump therapy, which maintains a "basal rate" of short-acting insulin in pulses delivered periodically through a tiny cannula inserted just under the skin, is an established standard of care for children and adults with Type 1 Diabetes [1], [2]. Insulin pumps, particularly automated insulin delivery (AID) pumps which communicate with or incorporate continuous glucose monitoring systems (CGMs), are associated with numerous benefits, including a lower incidence of hospitalization for diabetic ketoacidosis (DKA) compared to those that rely on multiple daily injections [3]. An estimated one million people are using commercial insulin pumps (CIPs) in the United States [4]. Notwithstanding these benefits, since 2013, >2.6 million adverse events (AEs) have been reported for insulin pumps (FDA product codes LZG, OYC, OZO, OZP, QFG) to the US FDA's Manufacturer and User Facility Device Experience (MAUDE) database [5], [6], [7]. See Fig. 1.

Many of these AEs are classifiable as hazards by the 2010 FDA Office of Science and Engineering Laboratories (OSEL) hazard analysis framework [8]. The principal hazards are insulin overdose leading to hypoglycemia, and insulin underdose leading to DKA. Delayed detection and notification of "occlusion without the user's awareness" was highlighted as an operational source of hazardous situations, together with underdose due to presence of air replacing insulin in the reservoir or delivery path—either of which can lead to hospitalization. For the purposes of this publication, the term "Silent Insulin Non-Delivery" (SIND) is defined as one or more of undetected or late-detection of occlusion, the presence of air instead of fluid in the delivery pathway, and leaking of fluid from the infusion site. Literature cites this as a longstanding, significant clinical and socio-technical concern for the diabetes community [9], [10]. A recent analysis of MAUDE database narratives confirms that the most frequent pump alarms associated with adverse events are for "occlusion" or "insulin flow blocked" [11]. The

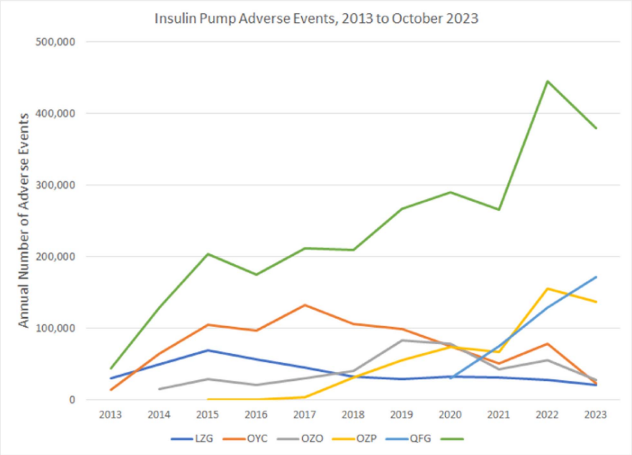

Fig. 1. Reported insulin pump adverse events, by FDA product code, 2013 to October 2023 [fda.gov].

authors speculated that the co-occurrence of occlusion alarms with hyperglycemia >400 mg/dL was *prima facie* evidence for *delayed* detection of insulin non-delivery and concluded that their findings supported calls to manufacturers to improve detection of occlusions and alarm systems to warn users in sufficient time to prevent adverse events.

Despite wide understanding of the burden of these hazards and adverse events, the underlying mechanical technology by which CIP manufacturers deliver insulin has not changed substantially in ∼30 years. Because they cannot directly detect flow of insulin, indirect, surrogate measures (i.e., sensors for pressure or motor load) are common technical strategies employed by CIP manufacturers to detect occlusion, but these secondary measures may fail to detect occlusion in a clinically relevant timeframe. Further, there is no regulatory requirement for insulin pumps to detect air in the delivery pathway [12].

Manufacturers are aware of the risks of SIND, and device labeling is replete with warnings that at clinically relevant insulin infusion rates, especially at the low basal flow rates for pediatric users, the detection of occlusion may not occur until after the onset of DKA [13]. The labeling also warns that extreme care must be taken by the user to avoid introduction of air when filling the reservoir, and to be aware that outgassing of air can occur as insulin warms (e.g., after refrigerated storage) or when ambient pressure falls (e.g., air travel). Current diabetes clinical management emphasizes user education, hypervigilance, and frequent manual and invasive blood glucose/ketone testing [14], [15], [16], [17].

An insulin pump recently cleared by FDA contains key inventions that result in a delivery mechanism with real-time precise flow measurement capability (ND) [18], [19]. The device provides rapid detection of insulin non-delivery due to delivery pathway occlusion, along with other advanced functionality as might be expected from the ability to automate adjustment of the volume and timing of insulin delivery pulses as required to manage blood glucose levels [18], [19].

The FDA clearance letter [19] for this new device (ND) reported improvement in key performance metrics over current FDA-reviewed sensor-augmented commercial insulin pumps (CIPs), including those from Medtronic MiniMed (600/700 series) (MM); Tandem Diabetes Care (t:slim X2) (TD); and Insulet (Omnipod) (OP).

We report the results of bench testing of the ND: a) to corroborate occlusion detection information that was included in the clearance letter and b) to gain a deeper understanding of the physical principles and capabilities of the detection mechanism as might pertain to possible incidences of site leakage reported in the marketplace. We also report the results of bench testing of the ND to evaluate the ability of the ND to perform in the presence of a common use error, air bubbles being introduced to the drug reservoir during filling, compared to the 3 CIPs.

The hypotheses under test were that the performance of ND (the device under test): a) is superior to CIPs in air management and occlusion detection; b) has been achieved without tradeoffs in required flow performance; c) is clinically relevant and could reduce the incidence of preventable adverse events and harm associated with SIND; and d) represents a platform that can be exploited to develop useful future functionality.

II. Materials and Methods

A. Materials

The device under test, the FDA-cleared ND, employs an acoustic sensor system to measure in real time the volume of insulin delivered with each delivery mechanism pulse. In other relevant aspects, the ND does not differ technically from currently available CIPs. See Supplementary Materials for specifications and images.

The ND under test was manufactured for SEQUEL MED TECH in Manchester, NH, USA. The CIPs—Medtronic (600/700 series; 3 devices) (MM); Tandem Diabetes Care (t:slim X2; 3 devices) (TD); and Insulet (Omnipod; 10 devices) (OP)—were set up following the respective device manufacturer's instructions.

B. Methods

Long and short-term flow accuracy, occlusion detection time/pressure, and air management capability were assessed for the ND, MM, TD, and OP following, where appropriate, Association for the Advancement of Medical Instrumentation (AAMI) standards [AAMI TIR101:2021 (TIR)], including PK-CV analysis, which includes a pharmacokinetic model with drug half-life (decay time) as a parameter.

Long and Short-term Flow Accuracy: Insulin (U100) flow at 0.1, 0.3, and 1.0 U/h from all 4 types of pumps was measured gravimetrically in alignment with AAMI test method TIR101 in an environmentally controlled test laboratory located on a thick concrete ground floor at nominal office temperatures of 21+/−2 °C and ambient pressure of 99–102 kPa. Calibrated analytic balances (Sartorius MCE2255-2S00-I, 0.00001 g resolution) were used to acquire mass data once every ten seconds. Balances were placed on a 63 kg granite slab set on a rubber vibration-damping cushion and mounted on a heavy metal stand inside a plexiglass housing. Insulin was collected in a 100 mL

TABLE I
ACCURACY TEST RUNS BY PUMP

Pump	Runs	Total hours
OP	9	557
MM	6	883
TD	13	1649
ND	9	970

glass beaker with the fluid outlet immersed below a 25 g layer of silicone oil to minimize evaporation. All liquid was acclimated to room temperature for >2 hr prior to testing. An insulin density of 1.004 g/mL was used for each run. Data was acquired using a purpose-built logger (Sartorius V3.2).

The logged mass data was analyzed using a purpose-built LabVIEW G-language virtual instrument (VI). During flow characterization experiments, mass measurements were recorded in grams, converted to volume in microliters (1.000 g/ml or 0.001g/µl) and summarized in IU insulin (100 IU Rapid Acting Insulin Analog (RAIA) / 1 ml or 0.1U/µl). Analysis routines computed metrics over hundreds of hours of delivery. The total number of runs and hours for each pump tested is shown in Table I. Long-term flow rate accuracy was computed using linear-least squares fit, and short-term variability was evaluated using the AAMI TIR101 "PKCV" method [20]. See (1)–(3) for the calculation of mean drug flow rate error. Flow data was processed using a one-compartment PK model which acts as a low-pass digital filter. The model approximates physiologically active levels of a drug with a half-life of 60 minutes.

To assess short-term variation (hour-to-hour), the coefficient of variation (CV%) was determined as the ratio of the sample standard deviation to the mean compartment volume over a stable region of the test. See (4)–(8) below.

See Supplementary Materials for schematics and further details of the PKCV methodology.

EQUATIONS for Mean and Short Term Flow Error

(1) *Mean Flow Rate error:* Refer to AAMI TIR101.

$$Q_i = \frac{M_i}{\rho} \tag{1}$$

where:
Q_i is the calculated volume of the sampled mass (mL);
M_i is the sampled mass (g);
ρ is the fluid density $\frac{g}{mL}$.

$$\hat{\beta} = \frac{\sum_{i=1}^{N} (t_i - \bar{t})\,(Q_i - \bar{Q})}{\sum_{i=1}^{N} (t_i - \bar{t})^2} \tag{2}$$

where:
$\hat{\boldsymbol{\beta}}$ is the estimated slope of a linear fit to the volume data $(\frac{\mathrm{mL}}{\mathrm{h}})$;
N is the number of samples evaluated;
t_i is the sampling time (h);
$\bar{t}$ is the mean sample time for i from 1 to N samples;
$\bar{Q}$ is the mean of the calculated volumes for i from 1 to N samples;
Q_i is the calculated volume of the sampled mass (mL).

$$E = \frac{\hat{\beta} - \dot{Q}P}{\dot{Q}P} \cdot 100\% \tag{3}$$

where:
E is the measured mean delivery rate error (%);
$\hat{\boldsymbol{\beta}}$ is the estimated slope of a linear fit to the volume data $(\frac{\mathrm{mL}}{\mathrm{h}})$;
$\dot{Q}\,P$ is the programmed delivery rate $(\frac{\mathrm{mL}}{\mathrm{h}})$.

(2) *Short-term drug flow error* using AAMI TIR101 pharmacokinetic-coefficient of variation (PKCV) method with 1 hour, single compartment model kinetics.

$$V_i = B \cdot V_{i-1} \tag{4}$$

computed for i from 1 to N samples
where:
V_i is the calculated volume in the 1-compartment pharmacokinetic (PK) model (mL);
B is the one-compartment recursion coefficient given by (6) (unitless);
V_0 is zero $(0\,\mathrm{mL})$ - initial volume of compartment.

$$CV = \frac{\sigma V}{\bar{V}} \cdot 100\% \tag{5}$$

where:
CV is the coefficient of variation of the compartment volume (%);
σV is the sample standard deviation computed over steady state as given by (7) (mL);
$\bar{V}$ is the mean of the calculated compartment volumes over steady state as given by (8) (mL).

$$B = e^{\frac{-T \cdot \ln(2)}{T_{\mathrm{half}}}} \tag{6}$$

where:
B is the PK one-compartment recursion coefficient (unitless);
T is ten seconds $(\frac{1}{360}h)$ the mass measurement sample period (h);
In (2) is used to convert half-life to time-constant;
T_{half} is one hour, the single-compartment half-life.

$$\sigma V = \sqrt{\frac{1}{N - N0} \sum_{i=N0}^{N} \left(V_i - \bar{V}\right)^2} \tag{7}$$

$$\bar{V} = \sqrt{\frac{1}{N - N0} \sum_{i=N0}^{N} V_i} \tag{8}$$

where:
N is the number of samples applied to the PK filter;
$N0$ is the first sample of the computed compartment volume for evaluation - allowing the computed compartment volume V to reach steady state flow;
V_i is the calculated volume in the 1-compartment pharmacokinetic (PK) model (mL)

Occlusion Detection Testing: Occlusion detection time at dose rates ranging from 0.3 to 1.0 U/h was measured in an

office ambient environment. Each pump's reservoir was filled to its nominal capacity with distilled water according to the instructions for use. Distilled water is consistent with current testing standards [20] for occlusion and air testing since its properties are similar to insulin. Delivery commenced at selected test infusion rates. Once flow was visually verified at the infusion set cannula, a hemostat was applied, and a stopwatch (Control Company 4-channel timer) was started. On alarm, the stopwatch elapsed time was recorded.

Occlusion Detection Pressure: Since the risk of fluid loss due to site leakage logically increases with increased hydraulic pressure, the maximum pumping pressure experienced during a blockage can serve as a key indicator of the risk of fluid loss during a site blockage. Pressure measurements were taken at time of occlusion for a set of runs performed using the same method described in "Occlusion Detection Testing", with the exception that a calibrated in-line pressure sensor [Heise Model "PM," range: −13.5 to 30 PSIG, accurary: +/−0.1% full scale] was placed between the pump and the location of the occlusion. Testing was performed at a programmed dose rate of 12.0 U/h.

Air Management Testing: The ability of the pumps to manage air introduced to the drug reservoir during filling by a user was assessed by replacing fluid volume in the filled drug reservoir with 0.2 mL of air. In each case, the volume of fluid and air present in the reservoir combined to match the maximum reservoir fill volume specified by the manufacturer. All pumps were fully primed without removing the included air. After priming, all pumps were oriented to promote air bubble migration to their reservoir outlet and delivery started at 15 U/hr. Each pump was observed to determine whether the pump detected the introduced air and alarmed, delivered the air without alarm, or managed to sequester the air in the reservoir without impacting delivery.

III. Results

Long-term basal flow rate error (average of all runs for each pump) was less for ND pump than for CIPs. Occlusion detection by ND ranged from 5 to 22.5 times faster than by the CIPs, depending on basal flow rate, and the pressure measured upon occlusion detection was 2 to 5 times lower for the ND. All CIP pumps could be observed to infuse air without detection while ND prevented air in the reservoir from being delivered.

Long-term Basal Flow Rate Accuracy: As shown in Fig. 2, the 3 CIPs showed a greater mean flow rate error than ND. The lowest basal rate (0.1 U/h) had the largest errors, with one exception, in that ND had a slightly larger error at 0.3 U/h than at 0.1 U/h). ND was the only pump with all errors less than +/−5%. The greatest over-infusion was 21.4% at 0.1 U/h by OP, and the greatest under-infusion was 10% by MM at 0.1 U/hr.

Short Term Basal Flow Rate Accuracy: Using PKCV to evaluate short-term variability of insulin bioavailability in the 1-compartment pharmacokinetic model (PK) model, and computing the results using a 60-minute half-life for rapid-acting insulin analog (RAIA), pumps MM, TD, and ND produced similar CV values that were larger (approximately 7%) at the lowest tested basal flow rate of 0.1 U/h. Pump OP produced noticeably higher CV% values, reaching 15% at 0.1 U/h. Comparing these results

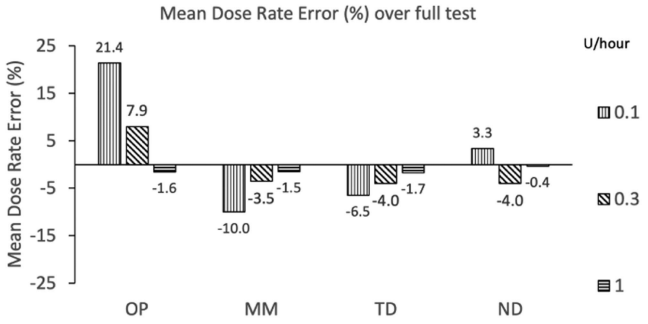

Fig. 2. Long-term basal rate accuracy over full test period. OP=Insulet (Omnipod), MM=Medtronic (600/700 series), TD=Tandem Diabetes Care (t:slim X2), ND=new pump. Note: the higher error at low flow rates is consistent with the literature on pumps that have a syringe-like insulin reservoir, which can disrupt flow uniformity, especially at low flow rates [24], [25].

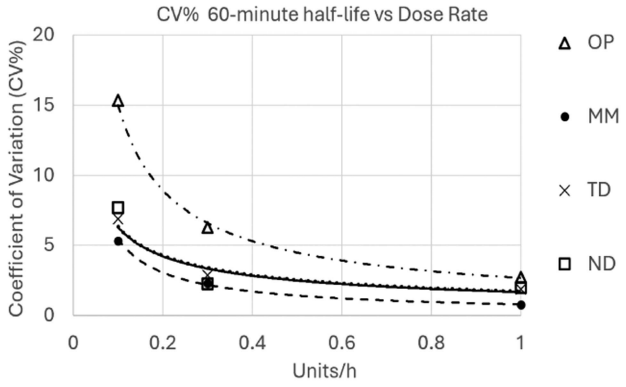

Fig. 3. Comparison of short-term insulin availability using AAMI-TIR101 PKCV method. OP=Insulet (Omnipod), MM=Medtronic (600/700 series), TD=Tandem Diabetes Care (t:slim X2), ND=new pump.

TABLE II
OCCLUSION DETECTION PRESSURES

Pump	Occlusion Pressure, psi (mean, min-max)
OP	23.62 (18.07-32.98)
MM	14.25 (14.02-14.55)
TD	20.77 (18.76-23.71)
ND	6.51 (6.39-6.59)

to the AAMI TIR101 guideline, the 7% variation is considered low or acceptable, and the 15% level unfavorable for medications requiring titration (see Fig. 3).

Occlusion Detection: Fig. 4 presents the data which shows the relationship between basal rate and occlusion detection time.

The data demonstrates that the ND produced a significant improvement of a 5 to 22.5-fold reduction in occlusion time over the CIP pumps.

Occlusion Detection Pressure: Line pressures measured at time of occlusion are shown in Table II above. Three runs were performed for each pump. Measurements were taken throughout the run with basal delivery set at 12 U/h. The data shows ND

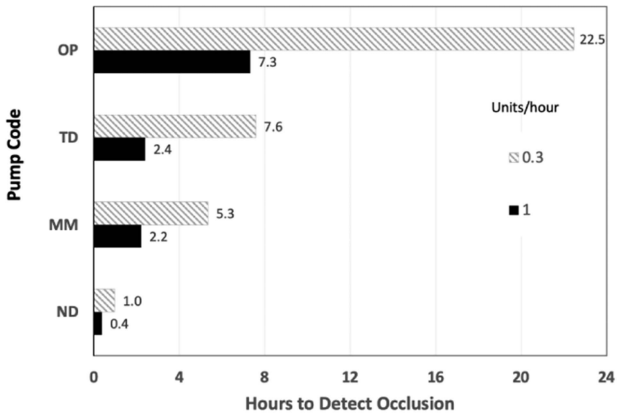

Fig. 4. Occlusion detection time vs. basal rate. OP=Insulet (Omnipod), MM=Medtronic (600/700 series), TD=Tandem Diabetes Care (t:slim X2), ND=new pump.

TABLE III
AIR MANAGEMENT OBSERVATIONS

Pump	Air Delivered?	Alarm Reported?
OP	Yes	No
MM	Yes	No
TD	Yes	No
ND	No	No

exhibits a substantial improvement in line pressure during blockages, with the competitors generating pressures of between double and triple ND's line pressures at the time of the alarm. These results suggest ND is better suited to detecting line blockages before they become site leaks and contribute to incidents of SIND.

Air Management: Each of the pumps was loaded with a full insulin reservoir that also contained 0.2 mL of air, primed and allowed to run at 15 U/h to empty. The data shows OP, MM, and TD pumps were able to deliver the reservoir air, without interruption or alarm, until the reservoir was completely empty, whereas ND continued to deliver fluid uninterrupted, neither alarming nor delivering the air placed in the reservoir. The results suggest ND has a mechanism for air sequestering functions to keep reservoir air from entering the infusion stream. Table III shows the observations made during each run.

IV. DISCUSSION

V. Adverse events related to silent insulin non-delivery (SIND) are frequent occurrences for insulin pump users, with 40–50% of users experiencing one or more such adverse events per year [22]. Survey data and pump downloads reveal that SIND may occur as frequently as once per month and is detected more frequently by chemical measurement of (or by symptoms of) hyperglycemia or DKA than by pump alerts or alarms [22], [23]. Adverse event analysis from the FDA MAUDE database confirms that the most frequent pump alarms associated with adverse events are for "occlusion" and "insulin flow blocked" [11]. Current troubleshooting and resolving delivery pathway faults is difficult, time consuming, error-prone, and potentially expensive for the user. In the absence of timely and accurate notification of occlusions, the user may ascribe hyperglycemia to other causes, unaware that insulin flow may have been interrupted due to cannula occlusion or leakage of medicine from the infusion site. By the time they have exhausted other possibilities or received an occlusion notification, they may be at heightened risk of DKA. The frequency of blood glucose values >400 mg/dL and/or hospitalization of users when delayed occlusion or "insulin flow blocked" alarms *do* occur, as extracted from MAUDE narratives, is real-world evidence consistent with manufacturers' labeling that warns of delayed detection of potentially life-critical events by legacy CIP pumps. Survey data confirms that SIND and other operational issues with CIPs are a persistent socio-technical burden on persons with diabetes and on caregivers, prompting "burnout" and "consideration of pump discontinuation" [22].

The technical mechanisms by which the ND and CIPs: a) deliver fluid in periodic pulses or delivery increments, and b) detect flow path occlusion or air were discovered by review of public information in patents or literature and by information requests to the ND's developers and test engineers. Bench testing of the ND and legacy OP, MM, and TD devices was conducted: a) to confirm flow accuracy measurements using several analytic approaches, b) to corroborate occlusion detection times published in the FDA clearance letter, c) to determine the extent to which pumps are more likely to generate leakage at the infusion site, and d) to characterize the ability of the pump to manage a foreseeable use error of air added to the drug reservoir during filling. Approximately 4145 hours of micro-gravimetric flow accuracy data were analyzed with respect to long-term flow rate error, and short-term-flow variability was computed using methods defined in AAMI TIR101. Although testing was limited to characterization of constant flow (basal delivery), the results are extensible to bolus delivery, in that a bolus may be considered a short-duration high basal rate. The ND's performance, with respect to long-term flow rate accuracy and PKCV, was superior to all of the commercial CIP samples included in the testing.

Test data revealed that for hard occlusions located at or near the delivery cannula, the ND was at least 5 times (at higher flow rates) and as much as 22.5 times (at lower flow rates) faster at detecting occlusion than the CIPs. Further, the line pressures at time of occlusion detection were substantially lower for the CIP. The new technology in the ND leads to heightened sensitivity to occlusion and lower line pressures, which collectively may offer a significant potential for reducing silent insulin non-delivery caused by site leakage. ND's unique acoustic volume measurement ability allows it to detect occlusions in the delivery path sooner and at much lower pressures than conventional CIP technology. In addition to much faster detection time, this ability may be able to alert the patient to the buildup of tissue obstruction at the catheter tip. Future testing will explore how the ND and CIPs respond to flow obstruction and transient occlusions.

With respect to air management, the 3 CIPs can be made to infuse air without detection when challenged with basic "foreseeable misuse," whereas the ND sequestered air within its drug reservoir and continued delivering unimpeded. Based on the encouraging air management data obtained for the ND, the

authors pursued an additional challenge of the ND to evaluate the potential limits of its air management capabilities. Six NDs were prepared for delivery in accordance with the air management test procedure, with the modification that the authors replaced 1.5 mL of insulin in the full reservoir with air instead of the previous air amount of 0.2 mL. Each ND was primed so as to preserve the air in the reservoir and then programmed to deliver insulin at 15 U/h. The units were monitored for air delivery and alarms throughout the expected 10-hour run duration. In all cases, the ND did not deliver the air from the reservoir, and instead delivered the full fluid contents of the drug reservoir. Once all fluid in the reservoir had been delivered, each ND appropriately generated an alarm, reporting the reservoir had emptied. These additional exploratory results suggest the ND incorporates a substantial capacity for sequestering air that may be present in the drug reservoir, as well as provides reliable and appropriate detection of, and alarm notification for, air entering the delivery mechanism. Further research is indicated.

V. Conclusion

This work assessed the long and short-term flow accuracy, occlusion detection time and pressure, and air management capability for a new insulin pump (ND) design versus 3 legacy pumps using standardized methods including AAMI TIR101 pharmacokinetic-coefficient of variability (PK-CV) analysis. The ND outperformed 3 legacy designs on long-term flow rate error, speed of occlusion detection, pressure at occlusion, and air management. These preliminary results do not constitute a full suite of tests on multiple ND and CIP devices, with sufficient duplicates suitable for full statistical analysis. Certain tests of performance with, for example, dynamic backpressure, or head height changes, were not completed. However, the results described herein are sufficiently promising to warrant investment in further research.

As automatic insulin delivery (AID) systems become more widely adopted, and fully closed loop (FCL) AID systems become a reality, the distinction between basal and bolus delivery will fade. Current commercial AID systems deliver variable amounts of insulin as often as every five minutes, based on frequent updates of estimated glucose values from CGMs, using insulin-delivery technology that has not changed since the early 1990s. As AID systems are more widely adopted by users, the importance of the ability of the system to detect fault conditions (especially partial, gradually increasing, or full occlusion, and/or the displacement of insulin by air) will increase dramatically. If such events are not known to the AID algorithm and taken into account or prevented through technologies such as that of the ND presented here, they may drive the systems into delivery oscillations that lead to hazardous and/or harmful situations. The ND, with its improved occlusion detection times and air management, along with its lower propensity towards site leakage, provides significant performance advantages over the CIPs. These improvements advance the state of the art in drug delivery and may likely enable a future reduction in adverse events caused by SINDs.

Supplementary Materials

Please see the Supplementary Materials for expanded discussion of the background, significance, and experimental methods, as well as photographs of the experimental set-up.

Author Contributions

RDB developed the test plan and attended and supervised the device testing at the test laboratory. NMS participated in the device testing, conducted the bulk of the literature search, and prepared initial drafts of the publication. Both authors participated in the writing and revision of the manuscript text.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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