EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
Control-IQ Technology
DECISION MEMORANDUM

A. DEN Number:

DEN190034

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for Control-IQ technology.

C. Manufacturer and Device Name:

Tandem Diabetes Care, Inc. and Control-IQ technology

D. Type of Test or Tests Performed:

Not applicable.

E. System Descriptions:

1. Device Description:

Control-IQ technology (Control-IQ, the device) is a software-only device intended for use by people with diabetes. The device controls insulin delivery from a compatible alternate controller enabled insulin pump (ACE pump) based on inputs provided by a compatible integrated continuous glucose monitor (iCGM) and inputs provided the user (e.g., carbohydrate intake, exercise, and sleep schedule). Control-IQ technology is meant to be installed on a compatible ACE pump.

Control-IQ technology works to control glucose towards a glucose target range of 112.5-160 mg/dL during normal use. Glucose targets are not customizable but can be changed by a user if sleep or exercise modes are set or announced. During sleep mode, this range is changed to 112.5-120 mg/dL, and it is changed to 140-160 mg/dL during exercise mode.

Control-IQ technology includes an integrated feature whereby iCGM values are automatically populated into the glucose field of the integrated bolus calculator when the Control-IQ technology is active (i.e., the device is operating in closed-loop mode). This feature is disabled when Control-IQ is turned off.

Using Control-IQ technology requires that users input their weight and their total daily insulin requirement, which should be established with the help of a health care provider before using the device.

2. Principles of Operation:

   Control-IQ technology predicts glucose levels 30 minutes in the future based on prior iCGM readings, insulin delivery history, and user input (e.g., carbohydrate intake, exercise, and sleep schedule) and uses that prediction to adjust insulin delivery. Control-IQ technology can be used to adjust or suspend basal insulin delivery every 5 minutes and automatically deliver correction boluses of insulin based on actual and predicted CGM sensor readings. Users must manually deliver meal boluses they can calculate using the integrated bolus calculator and can manually adjust insulin delivery (change basal rates and deliver insulin boluses) when the Control-IQ technology is active.

3. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ___X___ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes __X____ or No _____

4. Software:

   FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

   Yes___X____ or No_____

F. Regulatory Information:

1. Regulation section: 21 CFR 862.1356

2. Classification: Class II

3 Product code: QJI

4. Panel: 75, Clinical Chemistry

G. Indications For Use:

1. Indication(s) for Use:

   Control-IQ technology is intended for use with compatible integrated continuous glucose monitors (iCGM) and alternate controller enabled (ACE) pumps to automatically

increase, decrease, and suspend delivery of basal insulin based on iCGM readings and predicted glucose values. It can also deliver correction boluses when the glucose value is predicted to exceed a predefined threshold.

Control-IQ technology is intended for the management of Type 1 diabetes mellitus in persons 14 years of age and greater.

Control-IQ technology is intended for single patient use and requires a prescription.

Control-IQ technology is indicated for use with NovoLog or Humalog U-100 insulin.

2. Special Conditions for Use Statement(s):

This device is for prescription use only.

This pump is for use only with U-100 Humalog or U-100 NovoLog. Only U-100 Humalog and NovoLog have been tested and found to be compatible for use in the pump. Use of insulin with lesser or greater concentration can result in under delivery or over delivery of insulin. This can cause hypoglycemia (low BG) or hyperglycemia (high BG) events. Use of other drugs or medications can damage the pump and result in injury if infused.

The sponsor performed an evaluation of the Control-IQ technology and determined that it may not be safe for use in children under the age of six because Control-IQ technology has lower limits of total daily insulin (≥10 units) and weight requirements (≥55 lbs.). Therefore, the sponsor has included a warning in the labeling for this device as follows:

> "Tandem performed an evaluation of the Control-IQ technology and determined that it may not be safe for use in children under the age of six because Control-IQ technology has lower limits of total daily insulin and weight requirements. Therefore, Control-IQ technology should not be used in anyone under the age of six years old. Control-IQ technology should also not be used in patients who require less than a total daily insulin dose of 10 units per day or who weigh less than 55 pounds, as those are the required minimum values needed in order for Control-IQ technology to operate safely."

When the device is in closed loop mode, the integrated iCGM auto-population bolus calculator feature of Control-IQ automatically enters individual iCGM values (i.e., point values) into the glucose field of the manual bolus calculator (the calculator is not auto - populated with iCGM values when in open loop mode). The bolus calculator does not take trend information into account. Because iCGM point values are typically less accurate than self-monitoring blood glucose (SMBG) meter results, using iCGM point values alone without taking trend information into account may result in inaccurate bolus calculations. Therefore, the sponsor has included the following instruction in the labeling for this device as follows:

"When the CGM reading is automatically populated into the bolus calculator, only the current CGM reading is used to calculate the correction bolus. The trend arrow is not used in the dose calculation. Speak with your healthcare provider for recommendations on how best to utilize the arrows for your correction bolus dosing."

At the time of device authorization, compatible iCGMs include the following: Dexcom G6 iCGM

H. Standards Documents/Guidance Documents Referenced (if applicable):

ISO 14971:2007: Medical Devices - Application of Risk Management to Medical Devices FDA Recognition No: 5-40

ANSI/AAMI/IEC 62366-1:2015 Medical Devices – Application of usability engineering to medical devices

ANSI/AAMI HE75:2009 Human factors engineering, Design of medical devices

I. Performance Characteristics*:*

For the purposes of analytical and clinical validation testing, the Control-IQ technology was installed on the Tandem t:slim X2 insulin pump with interoperable technology (DEN180058), which was paired with the Dexcom G6 continuous glucose monitoring system (DEN170088). Details on the performance characteristics of these devices can be found in the public decision summaries for each device.

1. Analytical Performance:

   Not applicable.

2. Comparison Studies:

   Not applicable.

3. Clinical Studies:

   Pivotal Study:
   The sponsor conducted a controlled, prospective, multicenter pivotal clinical trial consisting of 168 subjects, with 112 subjects in the treatment arm using Control-IQ. The study enrolled subjects diagnosed with type 1 diabetes who were using insulin (either multiple daily injections (MDI) or pump therapy). The study included 6 months of follow-up on all enrolled subjects. The sponsor extended the study protocol for up to 15 months to continue use of Control-IQ in all participants after the cross-over from SAP to Control-IQ in order to gather additional safety data.

Prior to wearing investigational study devices, all study subjects were trained on the device. Subjects who did not currently use an insulin pump or did not use a Dexcom G4, G5, or G6 CGM with readings captured on at least 11 out of the previous 14 days at the time of enrollment were required to participate in a 14-day run-in phase. Subjects who had prior experience with the Tandem t:slim pumps and who had the required amount of CGM data available were given the option to skip the run-in phase. To enter the randomization phase of the trial, participants had to have obtained CGM readings on at least 11 out of the previous 14 days, and pump-naïve patients must have successfully used the study pump each day. Subjects were assessed for their knowledge of pump and CGM use prior to continuing to the randomization phase of the study. Subjects who were new to pump use had their insulin pump settings optimized during the run-in phase. Pump settings were reviewed and further optimized at weeks 2, 13, and 26 of the study.

A summary of the pivotal clinical study is provided in the following table (Control-IQ group abbreviated as CLC (closed-loop control)):

Study Feature	Description
Title	The International Diabetes Closed Loop (iDCL) Trial: Pivotal Trial of t:slim X2 with Control-IQ Technology
Summary	A randomized controlled trial of 6 month at home closed loop control (CLC) system vs. sensor-augmented pump (SAP).
Investigational Device	Control-IQ Technology
Objectives	The objective of the study is to assess efficacy and safety of a closed loop system (Control-IQ Technology) in a randomized controlled trial.
Study Design	Randomized Clinical Trial with 2:1 randomization to intervention with the closed loop system vs. sensor-augmented pump for 6 months.
Number of Sites	Seven US clinical sites
Population	There were 31 subjects who were 14 - 18 years old, and 137 subjects >18 years old. The age range was 14-71 years with 33 as the average. 22 of the CLC group were MDI users. The average baseline HbA1c was 7.6. Key Inclusion Criteria • Type 1 Diabetes • Ages 14 and older Key Exclusion Criteria • Use of any non-insulin glucose-lowering agents except metformin

Sample Size	168 participants completed the 6-month randomized trial, with 112 in the intervention arm and 56 in the control arm.
Treatment Groups	Randomized Trial • Intervention Group: t:slim X2 with Control-IQ Technology and Dexcom G6 iCGM. • Control Group: Sensor-augmented pump (SAP) with no automated insulin delivery, and Dexcom G6 iCGM.
Study Duration	6 months for primary study, and up to 15 months total with extension phase
Protocol Overview/Synopsis	Eligible participants not currently using an insulin pump and/or Dexcom G4, G5, or G6 CGM with minimum data requirements participated in a run-in phase of 2 to 8 weeks that was customized based on whether the participant was already a pump or CGM user. Participants who skip or successfully complete the run-in were randomly assigned 2:1 to the CLC group using t:slim X2 with Control-IQ Technology or the SAP group for 6 months.

Pivotal Study Safety Results:
No severe hypoglycemia events occurred in either arm of the study. One diabetic ketoacidosis (DKA) event occurred in the CLC group. This event occurred as the result of an infusion set failure.

Hyperglycemia / ketosis events not meeting the definition of DKA were reportable if they met one of the following criteria:

- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
- blood ketone level ≥1.0 mmol/L and communication occurred with a health care provider at the time of the event
- blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider

There were 13 hyperglycemia/ketosis events meeting the above reporting criteria in the CLC arm compared to 2 in the SAP arm.

Subjects in both study arms were provided with blood ketone meters for use at home. There were 14 recorded events (11 subjects) of blood ketone levels >1.0 mmol/L in the CLC arm compared to 15 recorded events (8 subjects) in the SAP arm.

A summary of all reportable adverse events observed during the study is provided in the following table:

Table 1: Adverse Events by Study Treatment Group (Pre- and Post-Randomization)

	Post - Randomization		Pre-Randomization
	CLC	SAP	
Hyperglycemia with Ketosis	12	2	1
Diabetic Ketoacidosis (DKA)	1	-	-
Hyperglycemia without Ketosis	1	-	-
Concussion	1	-	-
Otitis Externa	1	-	-
Bypass Surgery	1	-	-
Total:	17	2	1

There were two unanticipated adverse device effects (UADEs) during the study, each of which was related to problems with the device software and resulted in the study being temporarily suspended while the problem was investigated and resolved:

1. Inappropriate suspension of basal insulin and inappropriate correction bolus delivery. There were several instances of excess insulin delivery as a result of this device malfunction, however there were no patient adverse events reported (i.e., no severe hypoglycemia or other adverse events). The device problem was corrected with a software patch during the study.

2. Incomplete bolus request resulting in hyperglycemia/ketosis. As a result of this device malfunction, approximately 45 subjects experienced inappropriate insulin suspension. In one instance a subject developed ketosis (2.1 mmol/L) as a result, but the patient did not develop DKA. The device problem was corrected with a software patch during the study.

Pivotal Study Observed Results:
The data below describe how the device performed during the pivotal study.

The table below provides a summary of selected metrics for the study run-in period (baseline), and the results after study completion (post randomization).

Table 2: Available CGM readings, HbA1c, and mean glucose observed in the pivotal study

	Baseline		Post Randomization	
	CLC (n=112)	**SAP (n=56)**	**CLC (n=112)**	**SAP (n=56)**
Hours of glucose readings, Median (Q1, Q3)*	307 (285, 327)	306 (283, 320)	4267 (4133, 4348)	4141 (3922, 4280)
HbA1c, Mean ± SD	7.40 ± 0.96	7.40 ± 0.76	7.06 ± 0.79	7.39 ± 0.92
Mean Glucose (mg/dL), Mean ± SD	166 ± 32	169 ± 25	156 ± 19	170 ± 25

*Quartile 1, quartile 3

During the pivotal study, the amount of time subjects spent in different CGM glucose ranges was observed as described in the following tables:

Table 3: Time spent in different glucose ranges as observed in the pivotal study

	Baseline		Post Randomization	
	CLC (n=112)	**SAP (n=56)**	**CLC (n=112)**	**SAP (n=56)**
% time in range 70-180 mg/dL, Mean ± SD	61% ± 17%	59% ± 14%	71% ± 12%	59% ± 14%
% time below 70 mg/dL, Mean ± SD	3.58% ± 3.39%	2.84% ± 2.54%	1.58% ± 1.15%	2.25% ± 1.46%
% time below 54 mg/dL, Mean ± SD	0.90% ± 1.36%	0.56% ± 0.79%	0.29% ± 0.29%	0.35% ± 0.32%

Table 4: Time spent in different glucose ranges analyzed by time of day, post-randomization

	Daytime		Nighttime	
	CLC (n=112)	**SAP (n=56)**	**CLC (n=112)**	**SAP (n=56)**
Mean Glucose (mg/dL), Mean ± SD	158 ± 20	170 ± 26	150 ± 18	170 ± 27
% time above 300 mg/dL, Mean ± SD	2.6% ± 3.8%	4.8% ± 6.1%	1.8% ± 2.5%	4.5% ± 6.3%
% time above 250 mg/dL, Mean ± SD	7.6% ± 7.4%	12.4% ± 10.5%	5.4% ± 5.6%	12.3% ± 10.5%
% time above 180 mg/dL, Mean ± SD	28.6% ± 12.7%	38.3% ± 15.2%	22.5% ± 12.5%	39.1% ± 16.8%

% time below 70 mg/dL, Mean ± SD	1.64% ± 1.2%	2.21% ± 1.5%	1.44% ± 1.2%	2.38% ± 1.9%
% time below 60 mg/dL, Mean ± SD	0.59% ± 0.5%	0.72% ± 0.6%	0.60% ± 0.6%	0.85% ± 0.9%
% time below 54 mg/dL, Mean ± SD	0.28% ± 0.3%	0.32% ± 0.3%	0.32% ± 0.3%	0.44% ± 0.5%

Safety of CGM Auto-populating Bolus Calculator Feature:

The device includes a feature whereby iCGM values are automatically populated into the glucose field of the integrated bolus calculator when the Control-IQ technology is active (i.e., the device is operating in closed-loop mode). The bolus calculator only uses the iCGM point value. It does not use iCGM trend information. When the Control-IQ technology is turned off (i.e., the device is operating in open-loop mode) the CGM auto-populating feature is disabled and users must manually enter a blood glucose value. The iCGM auto-populating feature is an integrated component of the Control-IQ technology device and cannot be used as a stand-alone device.

The sponsor analyzed iCGM readings collected during the pivotal study to assess the safety of Control-IQ technology feature whereby iCGM point values are auto-populated into the integrated bolus calculator. iCGM readings up to 5 hours after a bolus was delivered were analyzed.

Two groups of bolus types were compared: (1) in which patients accepted the output of the bolus calculator based on the auto-populated iCGM value, with no modifications, and (2) in which patients manually adjusted the bolus calculation either by manually entering in a glucose value or manually altering the insulin dose recommendation. Results were stratified based on the iCGM value when the bolus was requested.

The following table presents the rates of low CGM glucose values observed within a 5-hour window after a bolus for boluses requested with various initial CGM values.

Table 5: Post-correction bolus CGM readings (5 hours): based on starting glucose values

iCGM Glucose Value	Entry Type	One or More iCGM Reading <54 mg/dL (95% CI)	Three Consecutive iCGM Readings <70 mg/dL	Five or More iCGM Readings <70 mg/dL (95% CI)
70–180 mg/dL	Automatic (n=8,700)	3% (2.8, 3.5)	7% (6.6, 7.6)	11% (10.3, 11.6)
	Manual (n=953)	5% (3.2, 5.8)	9% (7.4, 11.1)	13% (10.4, 14.6)
181–250 mg/dL	Automatic (n=6,071)	4% (3.9, 5.0)	9% (8.0, 9.4)	12% (11.3, 13.0)
	Manual (n=568)	5% (3.4, 7.1)	9% (6.6, 11.3)	12% (9.5, 14.8)
>250 mg/dL	Automatic (n=2,252)	5% (4.0, 5.8)	9% (7.5, 9.8)	13% (11.9, 14.7)
	Manual (n=384)	4% (2.4, 6.5)	7% (4.5, 9.6)	9% (6.5, 12.3)

In the above table, the differences observed between post-correction bolus iCGM readings for boluses calculated using automatically populated iCGM values and those calculated using manually entered glucose values were not significantly different for starting iCGM glucose values below 250 mg/dL. For boluses given when starting iCGM glucose values were >250 mg/dL, the rate at which subjects had five or more consecutive iCGM readings <70 mg/dL within 5 hours post-bolus was higher when subjects used the auto-populated iCGM value. To address this risk, the sponsor updated the user guide and the training materials for physicians and patients to include information and instructions explaining that the bolus calculator does not use trend information, and that users should read the iCGM user guide and consult with their healthcare providers to determine how to use iCGM trend information when using the bolus calculator.

Safety in the Pediatric Population

The sponsor provided a limited amount of safety data from an interim data analysis from an ongoing study in subjects 6-12 years old. There were no episodes of DKA or severe hypoglycemia reported. This device is indicated for use in people with diabetes 14 years of age and older.

In addition, the sponsor performed an evaluation of the Control-IQ technology and determined that it may not be safe for use in children under the age of six because Control-IQ technology has lower limits of total daily insulin (≥10 units) and weight requirements (≥55 lbs.). Therefore, the sponsor has included a warning in the labeling for this device as follows,

> "Tandem performed an evaluation of the Control-IQ technology and determined that it may not be safe for use in children under the age of six because Control-IQ technology has lower limits of total daily insulin and weight requirements. Therefore, Control-IQ technology should not be used in anyone under the age of six years old. Control-IQ technology should also not be used in patients who require less than a

total daily insulin dose of 10 units per day or who weigh less than 55 pounds, as those are the required minimum values needed in order for Control-IQ technology to operate safely."

Postmarket Surveillance Study

There is uncertainty remaining regarding the risk/benefit profile of the device when used in the broader intended use population. While the premarket clinical study provided to support the de novo authorization showed some benefits, the study included device users with relatively high levels of education relative to the general use population, and it was not adequately powered to assess differences in the rates of safety events (e.g., diabetic ketoacidosis and severe hypoglycemia). Furthermore, due to the nature of the study design, the apparent unfavorable difference in the rates of hyperglycemia/ketosis events (not rising to the level of severity of diabetic ketoacidosis) between the treatment and control arms may be due to reporting differences between users rather than a true difference from the device itself.

Accordingly, a postmarket surveillance study will be ordered by FDA to confirm understanding of safety and to evaluate the following question:

- What are the rates of diabetic ketoacidosis and severe hypoglycemia when the device is used in the real-world intended use population?
- Are there differences in the rates of diabetic ketoacidosis and severe hypoglycemia between the device users and standard of care?

To address these questions, the postmarket surveillance study will include:

- A prospective single arm cohort study with a minimum of 1,354 subjects being followed for one year to assess differences in the rates of severe hypoglycemia and diabetic ketoacidosis (DKA) between the treatment arm and current standard of care (based on valid scientific evidence of event rates in current standard of care including patients using multiple daily injection therapy, standalone insulin pumps, or sensor-augmented pumps not including pumps with automated insulin dosing features).
- A plan to collect robust data on the rates of severe hypoglycemia and DKA experienced by device users on a monthly basis throughout the study.
- Enrollment targets for specific populations of interest (i.e., pump naïve users, CGM naïve users, pediatric users, users with baseline HbA1c>8.5%).

4. Other Supportive Data Not Covered Above:

   a. Hazard Analysis:

      A comprehensive hazard analysis was provided for this device, in which design inputs and outputs, risks, and risk mitigations for software and interoperable hardware components associated with the safe and effective functioning of the device were reviewed. The hazard analysis provided in this submission accounted for the unique design elements, intended use, and risks of the Control-IQ technology. In particular,

this hazard analysis accounted for the risks associated with interoperability between the software device and the hardware device it was installed on, as well as with other third-party digital devices which met predefined criteria but were not specifically identified. This analysis identified hazards which could reasonably be anticipated to impact the proper use of the device, traced all identified risks to adequate design controls, and demonstrated that design features were appropriately implemented and validated.

b. Human Factors:

Human factors validation tests were conducted with the Control-IQ technology installed on the t:slim X2 insulin pump with interoperable technology (DEN180058). The summative human factors validation study was performed with sixty representative participants interactive with the device in a simulated use environment. All study participants received training that was consistent with the training that patients would receive with the commercial product. Usability evaluations assessed comprehension and usability of the device for critical device tasks. Results of the study demonstrated that the device could be used safely by intended users in the intended use environment when used in combination with a digitally connected device.

c. Insulin Compatibility:

The Control-IQ technology is designed to work with either Novolog or Humalog U-100 insulin. These insulins were used in the pivotal clinical study for this device and no other insulins have been tested for use with the device.

Other insulins should not be used with this device. Using insulins with different concentrations or different action profiles (e.g., PK/PD) with this device could result in under delivery or over delivery of insulin. This can cause hypoglycemia or hyperglycemia events.

d. User and Provider Training:

The sponsor provided detailed training materials for healthcare providers who will prescribe this device and manage patients who use this device. The training covers how the device works, details of the clinical study, setting up the device, and information on how to assess patient results with the device.

A training plan for device users was also provided. The plan provides resources for various types of users including new pump users, users switching from a different pump, and users upgrading from a Tandem device. The training plan includes live (in-person or remote) pump training for new pump users (optional for prior pump users) and required online training modules. The training includes initial start-up, troubleshooting, maintenance, and management of the device. Training includes a follow-up 3-5 days after the initial training and subsequent communication with that

person's healthcare provider to ensure ongoing follow-up care. Physician and user training as per the sponsor provided training materials is important to ensure safe use of the device.

e. Data Logging:

The sponsor provided validated software protocols which enable the device to record critical events, including information related to its state (e.g., commanded delivery rates/volumes, all algorithm calculations, open loop / closed loop mode, pump behavior, power on/off events), user inputs / key presses, and device settings (e.g., TDI, weight, sleep settings, and preferences). All log entries are time stamped, and the logs are either generated when the events occur or every five minutes in the case of recording algorithm calculations. These protocols were reviewed and found to be adequate.

f. Interoperability:

A plan and approach for interoperability were provided according to the FDA Guidance "*Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices - Guidance for Industry and Food and Drug Administration Staff*" and determined to be adequate to support and clearly specify expectations, requirements, and interface specifications to potential interoperable devices. In addition, the plans provided by the sponsor covered their approach to working with connected device companies regarding contractual issues, interfaces for data communication and exchange, and post-market reporting procedures and responsibilities (e.g., who is responsible for investigating and reporting complaints, malfunctions, and adverse events).

The sponsor additionally provided validated software protocols intended to ensure secure, accurate, and reliable communication with digital interfacing devices, as well as failsafe design features to mitigate the risks associated with interruption of communication with digitally connected devices. These protocols were reviewed and found to be adequate.

g. Cybersecurity:

Detailed information on cybersecurity of the device was reviewed and found to be acceptable. The sponsor also provided a software bill of materials, which provided details on all software used in the device and the hardware platform that the device was installed on. This included all manufacturer-developed, commercially licensed, open source, and off-the-shelf software components (including firmware as relevant), along with an identification of the hardware runtime environment in which each resides, with relevant version and/or model information, as well as details on whether each component was actively supported by its manufacturer or legacy licensed.

J. Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

K. Identified Risks to Health and Mitigations Measures

Identified Risk	Mitigation Measures
Patient harm due to inappropriate drug delivery	Clinical data demonstrating device performance Certain software validation testing User training plan Certain drug compatibility information in labeling
Risk due to poorer or different performance in pediatric populations	Clinical data demonstrating device performance in pediatric population Certain warning statements and precautions in labeling
Risk due to the inability of the controller to handle different pharmacokinetic/pharmacodynamic characteristics of the drugs	Clinical data demonstrating device performance Drug compatibility information in labeling User training plan Human factors testing
Risk due to lack of compatibility of connected devices	Certain validation of communication specifications, processes, and procedures with digitally connected devices Limitations on interoperable devices
Risk of connected devices having inadequate performance to allow safe use of the controller	Specifications for performance of connected devices Certain validation of communication specifications, processes, and procedures with digitally connected devices Limitations on interoperable devices
Failure to report device malfunctions or adverse events to the device manufacturer	Plans and procedures for assigning post-market responsibilities.
Risk of latent flaws in software	Robust software validation testing Certain validation of communication specifications, processes, and procedures with digitally connected devices Certain verification and validation of risk control measures
Failure to provide appropriate treatment due to loss of communication with connected devices	Certain verification and validation of risk control measures Certain validation of communication specifications, processes, and procedures with digitally connected devices

Identified Risk	Mitigation Measures
Risk due to insecure transmission of data	Certain validation of communication specifications, processes, and procedures with digitally connected devices
Failure to correctly operate the device	Human factors testing User training plan Compatible devices listed in labeling Certain warning statements and precautions in labeling
Failure to correctly determine the root cause of device malfunctions	Certain verification and validation of logging capability
Risk due to data transmission interference/electromagnetic disturbance	Certain verification and validation of electrical safety, electromagnetic compatibility, and radio frequency wireless testing

L. Benefit/Risk Analysis

Control-IQ technology is intended to be used with a compatible iCGM and ACE pump to automatically increase, decrease, or suspend basal insulin based on current and predicted glucose values. It can also deliver an automatic correction bolus when the glucose value is predicted to exceed a predefined threshold under specific conditions. Glucose targets are not customizable but can be changed by a user if sleep or exercise modes are set or announced. The device is indicated for patients with type 1 diabetes 14 years and older.

Users of the Control-IQ device had a percent time in iCGM range 70-180 mg/dL of 71% in the randomization phase of the trial; however, percent time in iCGM range 70-180 mg/dL is not a validated surrogate marker for clinical diabetes outcomes. Hemoglobin A1c (HbA1c) in the Control-IQ group was slightly improved compared to baseline values, and it does not appear that changes in HbA1c would be worse in patients using Control-IQ compared to patients using SAP. Subjects completed a series of questionnaires and surveys before and after the randomization phase of the study to assess changes in various quality of life aspects. In general, Control-IQ users reported reductions in diabetes related distress and fear of hypoglycemia. The device can suspend insulin delivery overnight to reduce the risk of nighttime hypoglycemia, which may provide quality of life improvement to device users and caregivers of device users. These aspects of the data collected indicated there may be significant benefits to patients from using the Control-IQ device.

The study was limited to subjects 14 years and older, thus safety and effectiveness was not demonstrated in children younger than 14. The device is indicated for use in subjects 14 years of age and older. Additionally, most of the study population had high socioeconomic and educational status which is likely not generalizable to the intended use population. As a result of the residual uncertainty regarding the generalizability of the study results a postmarket study will be performed for this device to confirm device safety in a broader population.

The risks associated with use of the Control-IQ technology in conjunction with the iCGM and ACE pump include hypoglycemia, severe hypoglycemia, hyperglycemia, and diabetic

ketoacidosis (DKA). These events can be attributed to software malfunctions with subsequent over-delivery or inappropriate suspension/under-delivery of insulin commands. Other factors can include erroneous iCGM data transfer with subsequent inappropriate insulin delivery or lack of insulin delivery, interoperable device communication/connectivity issues resulting in temporary loss of Control-IQ use, lack of user knowledge and training leading to device misuse, and a potential increase in mechanical problems that could compromise glycemic control if frequent infusion set failures occur leading to interruption of insulin delivery.

In the clinical study, there was one episode of DKA and no severe hypoglycemia events. The rate of severe hypoglycemia or DKA is difficult to ascertain given these are relatively infrequent events and the study was limited to 168 participants with 6-month device use duration. There appears to be a higher risk of hyperglycemia with ketosis based on the study event criteria; however, it is unclear if the higher rate of hyperglycemia and ketosis events in the CLC arm compared to the SAP arm is directly related to use of the Control-IQ device. The rate of reportable ketosis events as defined in the study protocol was higher in the Control-IQ arm; however, the number of measured ketosis events $\geq$ 1 mmol/L ketones (many of which were not recorded as study reportable events because the subjects did not report the event to a healthcare provider) was similar between both arms. Therefore, there is uncertainty about whether this is a true difference or a study artifact. Overall, there was one DKA event, caused by infusion site failure, observed in the Control-IQ group, however twice as many participants were randomized to Control-IQ compared to SAP and the DKA event may not be directly associated with the device. The rate of other adverse events appears to have been similar between the two study arms when accounting for possible differences in reporting. While the study was not statistically powered to demonstrate statistical superiority, the results suggest that the Control-IQ device may offer several benefits compared to use of a SAP including possible improvements in several measures of diabetic control such as HbA1c and blood glucose concentrations. Given that the study was not adequately powered to assess these specific improvements, or to assess the rates of rare events such as DKA and severe hypoglycemia, collection of additional data in the post-market space can confirm the safety of the device during real-world use.

The sponsor has demonstrated that the probable benefits of Control-IQ technology outweigh the probable risks in light of the special controls for this device type and in combination with general controls. The special controls for this device type are intended to provide reasonable assurance of the safety and effectiveness of the device in the hands of the intended users.

M. Patient Perspectives

Patient perspectives considered include information provided directly to the Agency by patients in written statements and also obtained through discussion with patients and patient advocacy groups at public forums regarding patient experiences with automated insulin dosing systems and digitally connected diabetes devices. This device will allow patients, in conjunction with their healthcare providers, to have more choice in the automated insulin dosing algorithm that integrates with other elements of their diabetes management strategy and works best for their body and their care. In addition, availability of this device will

facilitate agile technology development that will ultimately provide innovative diabetes diagnostics and therapies to patients more quickly.

N. Conclusion

The De Novo request is granted and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code: QJI
Device Type: Interoperable automated glycemic controller
Class: II (special controls)
Regulation: 21 CFR 862.1356