FDA Executive Summary

Prepared for the
July 21, 2016 meeting of the
Clinical Chemistry and Clinical Toxicology Devices Panel
P120005/S041
Dexcom G5 Mobile Continuous Glucose Monitoring System
Dexcom, Inc.

I. Introduction

This document is the **FDA Executive Summary** for the meeting of the Clinical Chemistry and Clinical Toxicology Devices Advisory Panel meeting on the Dexcom G5 Mobile Continuous Glucose Monitoring System (hereafter known as G5 CGM) from Dexcom, Inc. The sponsor (Dexcom) has submitted a supplemental application to their premarket approval (PMA supplement – P120005/S041) to add a new indication for use. The G5 CGM is currently intended to measure glucose in interstitial fluid as an adjunctive device to complement, not replace, information obtained from blood glucose monitoring devices (e.g., self-monitoring blood glucose meters, which measure glucose concentrations from capillary blood). Dexcom seeks FDA approval to claim that the G5 CGM can be indicated "to replace fingerstick blood glucose testing for diabetes treatment decisions." The submission is under review by the Division of Chemistry and Toxicology Devices (DCTD), Office of *In vitro* Diagnostics and Radiological Health (OIR), within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This document will provide background on continuous glucose monitoring systems (CGMs) and the clinical studies and other information Dexcom has submitted in support of this new indication. FDA is seeking the panel's opinion on whether Dexcom has provided adequate information to support the safe and effective use of the G5 CGM to replace blood glucose testing at home by people living with diabetes.

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III.   Dexcom G5 Mobile Continuous Glucose Monitoring System

The G5 CGM consists of a glucose sensor (for detecting interstitial fluid glucose), a transmitter that converts sensor glucose signals to glucose concentrations and transmits the calculated values to display devices, and a receiver device that displays the glucose concentration received from the transmitter (display devices are either the Dexcom receiver or a mobile device featuring a Dexcom app).

The glucose sensor used in the G5 CGM was originally approved in 2012 (under P120005) for use in the Dexcom G4 Continuous Glucose Monitoring System (G4 CGM). A modified algorithm that improved the point accuracy of the G4 CGM was approved in October of 2014 (P120005/S018) for adults and May of 2015 (P120005/S031) for children older than 2 years old. This algorithm change resulted in improved accuracy performance, and was validated in clinical trials provided in support of the noted PMA files to FDA. The G5 CGM has a modified transmitter and receiver compared to the G4 CGM, but senses or calculates glucose concentrations in the same way. The same clinical data was used to support accuracy of both the G4 and G5 CGMs.

IV.   Background

i.   *Diabetes mellitus*

Diabetes mellitus is a group of metabolic disorders characterized by poor physiological glucose control. Two major classes of diabetes, which differ in etiology, are prevalent in the population: Type I and Type II diabetes. Type I diabetes is predominantly characterized by loss of function of the insulin-producing beta cells of the islets of Langerhans in the pancreas, due to T-cell-mediated autoimmune destruction. Type II diabetes is characterized by the inability of an individual to respond adequately to normal levels of insulin (insulin resistance) and beta cell dysfunction (decreased insulin production). Acute complications of diabetes include hyperglycemia, which when untreated can lead to hyperglycemic emergency, including diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS), as well as severe hypoglycemia, which can lead to loss of consciousness, seizures, or death. Long-term complications of diabetes include cardiovascular disease, cerebrovascular disease, peripheral vascular disease, nephropathy, neuropathy, and retinopathy. Long-term prognosis varies according to individual factors, including disease duration and glycemic control.

Diabetes is controlled through diet and exercise, and, for Type I and insulin-dependent Type II patients, daily subcutaneous administration of insulin through subcutaneous injections or continuous subcutaneous infusion (insulin pump).. Insulin dosages should be calculated with as much accuracy as possible to avoid acute complications. These calculations may include several factors, including the individual's current blood glucose level, desired target glucose level, insulin sensitivity factor (ISF - how much their glucose drops per unit of insulin), insulin-to-carbohydrate ratio (ICR - how much insulin needed to account for a given quantity of carbohydrates), the type of insulin (e.g., fast-acting or long-acting), and physiological factors (e.g., exercise and sickness). Young children with diabetes are managed by caregivers with varying expertise and knowledge of diabetes (e.g., parents, school nurses,

teachers/daycare workers) until the user is mature enough to make these management decisions alone.

### ii. *Devices for home glucose measurement*

Most patients with diabetes need to monitor their glucose levels on a frequent basis: typically several times a day. These measurements are meant as a means to monitor the user's glucose levels when they are experiencing potential side effects of low or high glucose concentrations, but also when they are asymptomatic, since maintaining glucose levels near optimal levels is essential to prevention of complications. For example, one would test blood glucose, and if the value is too low, they would treat hypoglycemia to raise their blood sugar. For patients with insulin-dependent diabetes, a high blood glucose concentration is used to calculate the insulin dose needed to bring them into a more optimal range (euglycemia). If inaccurate blood glucose values are used to make treatment decisions, a patient may over- or undertreat which may result in adverse events (e.g., over-treatment with insulin based on a falsely high glucose result may result in severe hypoglycemia). The high frequency of daily glucose determinations can practically only be conducted with devices intended for home-use. There are currently two types of devices intended to help people with diabetes monitor their blood glucose values at home: Self-monitoring blood glucose meters (SMBG) and CGMs.

SMBGs directly measure blood glucose concentrations in capillary blood collected from the finger. These devices have improved over many decades to become more user-friendly and provide relatively accurate results. Generally, SMBG results are within 20% of the true blood glucose concentration in euglycemic and hyperglycemic samples. In hypoglycemic samples ($\leq$ 75 mg/dL glucose), SMBG results are generally within 15 mg/dL of the true blood glucose concentration. People with insulin dependent diabetes typically monitor by SMBG 3-10 times per day, and in addition to regular monitoring, are advised to do so prior to calculating an insulin bolus (e.g., to correct hyperglycemia, and/or to account for meal carbohydrates). People with Type II diabetes typically perform fewer SMBG measurements per day.

CGMs provide a "continuous" series of glucose readings (typically a new glucose reading is determined every few minutes). This continuous monitoring is accomplished by a sensor that is temporarily implanted under the skin (throughout a typical wear period of 7 days) that measures the glucose concentration in interstitial fluid rather than blood. In addition, to glucose readings, CGMs have additional features which provide additional information to the user. Real-time interstitial glucose results may then be displayed along with a trend line graph for recent past glucose level readings. Trend information provides the direction of the current glucose trend and approximate rate of change (see figure 1 below depicting the Dexcom G5 Mobile Continuous Glucose Monitoring System receiver). CGMs also have alerts which may alert the user to a high or low glucose value, or a predicted high or low glucose value.

Figure 1: Dexcom G5 CGM display. The status bar reports the current, real-time glucose value as well as a trend arrow, whose direction informs the user about the glucose trend direction and rate (i.e., glucose is 202 mg/dL and rising in this example). The glucose

information window provides the glucose trace graph (tracking information) for the previous several hours.
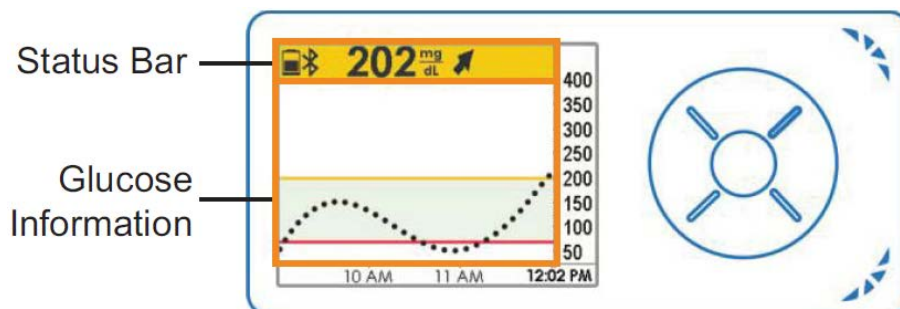
As mentioned above, in addition to tracking and trending information, CGMs provide users with real-time alerts and alarms (e.g., alarms that sound when current glucose values exceed pre-set glucose thresholds). For example, when a user's glucose values go below a pre-set low glucose threshold (e.g. below 70 mg/dL), an alarm will notify the user of this event. Thresholds for high glucose can typically also be set (e.g., when glucose values rise above 350 mg/dL). Together these features allow users to more passively monitor their glucose levels between pre-planned times for monitoring with SMBG, providing users with a level of reassurance.

Currently, CGMs are indicated for use in conjunction with SMBG, and CGMs' instructions for use state that users require a SMBG to verify the CGM reading prior to making treatment decisions. In addition, all currently-approved CGMs, including the G5 CGM, require calibrations using blood glucose values obtained with a SMBG (note that there is no FDA requirement that this must be the mode of calibration). CGMs allow users and their healthcare providers to evaluate historical glucose trends to help adjust disease management strategies. For example, users can view daily glucose peaks and troughs, glucose trends while sleeping, glucose rates of change, and potentially correlate those features to diabetes management activities.

The first Continuous Glucose Monitoring System (Medtronic Minimed) was approved for the U.S. market in 1999. In the years following, other device manufacturers received FDA approval for their CGMs (e.g. Dexcom received approval for their first CGM, the STS CGM, in 2006). Early devices were prone to interferences from ascorbic acid, uric acid, and acetaminophen, and had significantly inferior accuracy performance compared to current CGMs (see figure 2 below for comparison of the accuracy performance of the Dexcom STS, approved in 2006, to the Dexcom G5 Mobile Continuous Glucose Monitoring System, modified algorithm, approved in 2014).

Figure 2: Agreement (%) between CGM sensor-Reference paired points within various CGM glucose ranges

Reference Glucose Concentration	Percent Agreement to Reference Dexcom STS			
	40-80 mg/dL	81-120 mg/dL	121-240 mg/dL	241-350 mg/dL
Dexcom STS Concurrence	56%	44%	46%	65%

Reference Glucose Concentration	Percent Agreement to Reference Dexcom G5 CGM					
	40-60 mg/dL	61-80 mg/dL	81-180 mg/dL	181-300 mg/dL	301-350 mg/dL	351-400 mg/dL
Dexcom G5	89%	91%	92%	93%	94%	92%

SMBG devices provide relatively accurate blood glucose concentrations to use for treatment decisions, but they only provide a snapshot in time. Blood glucose values are constantly changing (e.g., +/- 2 mg/dL/min), and the rate of change can be considerable at times (glucose rates of change up to +/- 5 mg/dL/min were observed in Dexcom's clinical trial). If an individual's glucose was dropping at -3 mg/dL/min, and if they took 10 minutes to calculate and deliver an insulin bolus, they could be 30 mg/dL lower than expected at the time of injection.

CGMs are less accurate than blood glucose measurements (particularly in children), and there may be a lag between the blood glucose value and the interstitial glucose value at times when blood glucose concentrations are rapidly changing[1]. Inaccurate glucose results may lead to inappropriate treatment decisions that, as described above, may lead to adverse events or diabetes complications. However, CGMs provide additional information in the form of continuous trends that may reduce the negative impact of a more inaccurate point estimate of glucose concentration.

The G5 CGM is contraindicated for use by users taking acetaminophen, as this drug has been shown to falsely raise sensor glucose readings. The level of interference by acetaminophen may depend on individual factors as well as the concentration of acetaminophen; however,

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[1] Keenan D.B., Mastrototaro J.J., Voskanyan G., and Steil G.M. Delays in minimally invasive continuous glucose monitoring devices: a review of current technology. *J Diabetes Sci Technol.* 2009. Sep 1; 3(5):1207-14.

this interference can be significant enough to mask a user's actual glycemic state. A recent study demonstrated that participants wearing a Dexcom G4 CGM (which uses the same sensor as the G5 CGM), who ingested 1,000 mg of acetaminophen observed normal CGM readings even though their SMBG readings indicated that they were hypoglycemic, and some others observed high CGM readings even though their SMBG reading indicated that they were not hyperglycemic[2]. CGMs are also contraindicated for use during MRI, CT scans, or diathermy treatment.

Certain populations were not included in the clinical trials conducted in support of approval of CGMs: notably, pregnant women and severely ill hospitalized patients. Pregnant women were not included for safety reasons, due the exercise and glycemic challenges performed during conduct of these trials. Critically ill individuals may be exposed to any number or combination of treatments that were not feasible to include in the clinical trials for currently marketed CGMs. Sponsors have not sought FDA approval in these populations.

iii.   Use of CGM as a Replacement for SMBG

Throughout the past decade, CGM manufacturers have thought of the "replacement claim" as a major goal of research and development. In discussions with FDA about how to obtain this replacement claim, these manufacturers focused on point accuracy compared to SMBG as the potential endpoint for studies to support this claim (e.g., using the SMBG accuracy criteria in ISO 15197[3]). However, perhaps because of limitations of interstitial sensor technology, or fundamental differences in interstitial glucose compared to blood glucose, CGMs have remained less accurate than SMBG when assessed by individual paired glucose measurements despite significant improvements in CGMs accuracy over the past 5 years. As sensors became more accurate, FDA encouraged sponsors to think beyond point accuracy and propose other ways to support CGM "accuracy" and safety for this use, including the consideration of how trend information may mitigate the lower point accuracy of CGMs.

Beginning in August of 2014, Dexcom and FDA had a series of pre-submission meetings to discuss this issue. During these meetings, FDA and Dexcom discussed the type of prospective clinical study that would be necessary to demonstrate how these sensors performed in a broad population of people with varying physiology, environment, and behavior. It was apparent that the type of study that would generate statistically-meaningful clinical data support this new indication may not be feasible to conduct. This is because the clinically-relevant endpoints (e.g., severe hypoglycemia, DKA) are relatively rare and the types of clinical situations that may present risks to patients are so varied that they could not be captured in a short trial and a small population. Therefore, FDA suggested that, *in lieu* of premarket clinical trial data, the sponsor may be able to demonstrate a reasonable likelihood of safety and effectiveness of using the Dexcom G5 CGM as a replacement for SMBG

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[2] Maahs, D.M., DeSalvo, D., Pyle, L., Ly, T., Messer, L., Clinton, P., Westfall, E., Wadwa, R. P., and Buckingham, B. Effect of Acetaminophen on CGM Glucose in an Outpatient Setting. *Diabetes Care*. 2015, Oct; 38(10): 158-9.

[3] ISO 15197 - "In vitro diagnostic test systems — Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus"

measurements for dosing insulin via a combination of approaches: clinical data demonstrating sensor accuracy, *in silico* modeling of sensor performance in a broad population and in various use scenarios, a robust human factors assessment to demonstrate that users understand how to use the device safely, and a post-approval confirmatory study.

FDA suggested that if Dexcom were to attempt to use *in silico* modeling as part of the data they would propose in support of this new indication, FDA requested that Dexcom include *in silico* experiments that varied the physiological, behavioral, and environmental conditions for safe and effective use, and that could define the device's minimum performance characteristics required for safe and effective use (e.g., at what point is the sensor not safe for this use?).

According to statistician George Box, "All models are wrong, but some are useful[4]." *In silico* modeling, by necessity, incorporates assumptions that may not reflect variables (user, physiological, and/or device performance) that would be encountered in real-world use. In section V below, we describe the models Dexcom used, including the assumptions inherent in the models, and the results of the *in silico* studies. In addition to input on whether *in silico* modeling, generally, is adequate to demonstrate the safety and effectiveness of this device for this new use, FDA seeks the Panel's input on the adequacy of the particular *in silico* models used, the assumptions made by Dexcom in generating the models, and the simulations they provided to support this device claim.

V.   Summary of Clinical Trial and In silico Study Data

i.   G5 CGM accuracy clinical trial

As stated above, Dexcom used the clinical data generated on the G4 CGM to support accuracy of the G5 CGM since both systems use an identical glucose sensor and identical algorithms for converting sensor signal into glucose concentrations. The accuracy data for pediatric (ages 2-21 years) and adult (ages >21 years) subjects are summarized below in tables 1-3. Full descriptions of the accuracy of the sensor may be found in the Summary of Safety and Effectiveness Data documents for P120005/S018 (adults - http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S018B.pdf) and P120005/S031 (pediatric - http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S031B.pdf).

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[4] Box, G. E. P. (1979), "Robustness in the strategy of scientific model building", in Launer, R. L.; Wilkinson, G. N., Robustness in Statistics, Academic Press, pp. 201–236.

Table 1: Percentage of Dexcom G5 CGM readings that are within ±15 mg/dL, ±20 mg/dL, ±30 mg/dL, or greater than ±40 mg/dL of the reference (Ref) laboratory analyzer (for sensor readings less than 80 mg/dL), or within ±15%, ±20%, ±30%, or greater than ±40% of ref (for sensor readings greater than 80 mg/dL), in adult and pediatric study subjects.

CGM Glucose Range (mg/dL)	Population	Number of paired CGM-Ref readings	Percent within 15/15% Ref	Percent within 20/20% Ref	Percent within 30/30% Ref	Percent greater than 40/40% Ref
Overall	Pediatric	2262	81%	91%	96%	2%
	Adult	2263	86%	93%	98%	1%
40-60	Pediatric	86	54%	74%	91%	3%
	Adult	120	89%	94%	98%	0%
61-80	Pediatric	142	77%	82%	90%	3%
	Adult	226	91%	96%	99%	0%
81-180	Pediatric	805	78%	88%	97%	1%
	Adult	738	84%	92%	98%	1%
181-300	Pediatric	957	89%	96%	99%	1%
	Adult	798	86%	93%	98%	1%
301-350	Pediatric	209	81%	91%	94%	5%
	Adult	229	86%	94%	98%	1%
351-400	Pediatric	63	64%	81%	83%	8%
	Adult	152	80%	92%	97%	0%

Tables 2a and 2b: Concurrence of CGM Readings and Reference Values in adult and pediatric study subjects. The tables are arranged by each CGM glucose range (first column) and tabulate, for each range of CGM glucose readings, the percentage of paired Yellow Springs Instrument reference values that were in the identical glucose range (shaded diagonal), as well as those reference values that were in glucose ranges above and below the paired CGM readings.

Table 2a: Concurrence of G5 CGM Readings and Reference Values in adult study subjects.

CGM mg/dL (mmol/L)	Number of Paired CGM-Ref	Percent of matched pairs in each Ref glucose range for each Sensor glucose range Ref mg/dL (mmol/L)										
		<40	40-60	61-80	81-120	121-160	161-200	201-250	251-300	301-350	351-400	>400
<40	18	6%	83%	11%	0%	0%	0%	0%	0%	0%	0%	0%
40- 60	120	2%	74%	22%	3%	0%	0%	0%	0%	0%	0%	0%
61- 80	226	0%	19%	68%	13%	4%	0%	0%	0%	0%	0%	0%
81- 120	347	0%	0%	19%	72%	8%	1%	0%	0%	0%	0%	0%
121- 160	246	0%	0%	0%	17%	72%	11%	0%	0%	0%	0%	0%
161- 200	286	0%	0%	0%	0%	25%	59%	16%	0%	0%	0%	0%
201- 250	376	0%	0%	0%	0%	0%	16%	70%	13%	1%	0%	0%
251- 300	281	0%	0%	0%	0%	0%	2%	16%	61%	14%	7%	0%
301- 350	229	0%	0%	0%	0%	0%	0%	2%	28%	59%	10%	1%
351- 400	152	0%	0%	0%	0%	0%	0%	0%	4%	47%	45%	5%
>400	45	0%	0%	0%	0%	0%	0%	0%	0%	20%	38%	42%

Table 2b: Concurrence of G5 CGM Readings and Reference Values in pediatric study subjects.

CGM mg/dL (mmol/L)	Number of Paired CGM-Ref	Percent of matched pairs in each Ref glucose range for each Sensor glucose range Ref mg/dL (mmol/L)										
		<40 (<2.2)	40-60 (2.2-3.3)	61-80 (3.4-4.4)	81-120 (4.4-6.7)	121-160 (6.7-8.9)	161-200 (8.9-11.1)	201-250 (11.1-13.9)	251-300 (13.9-16.7)	301-350 (16.7-19.4)	351-400 (19.4-22.2)	>400 (>22.2)
<40 (<2.2)	16	6%	25%	63%	6%	0%	0%	0%	0%	0%	0%	0%
40-60 (2.2-3.3)	86	0%	33%	60%	6%	1%	0%	0%	0%	0%	0%	0%
61-80 (3.4-4.4)	142	0%	8%	64%	26%	2%	0%	0%	0%	0%	0%	0%
81-120 (4.4-6.7)	314	0%	1%	15%	69%	13%	1%	1%	0%	0%	0%	0%
121-160 (6.7-8.9)	313	0%	0%	0%	15%	66%	18%	1%	0%	0%	0%	0%
161-200 (8.9-11.1)	355	0%	0%	0%	1%	18%	66%	15%	0%	0%	0%	0%
201-250 (11.1-13.9)	444	0%	0%	0%	0%	1%	17%	68%	14%	0%	0%	0%
251-300 (13.9-16.7)	336	0%	0%	0%	0%	0%	0%	26%	58%	16%	0%	0%
301-350 (16.7-19.4)	209	0%	0%	0%	0%	0%	0%	4%	40%	46%	9%	0%
351-400 (19.4-22.2)	63	0%	0%	0%	0%	0%	0%	3%	14%	62%	21%	0%
>400 (>22.2)	24	0%	0%	0%	0%	0%	0%	4%	13%	29%	38%	17%

Based on clinical study data, the accuracy of the G5 CGM compares favorably to the other major system on the market, the Medtronic Enlite sensor (part of the 530G Threshold Suspend System). The clinical data for the Medtronic 530G (see figure 3, below) were provided in support of PMA approval P120010, in subjects ages 18 years and older. Note that though the trials had very similar study designs, the Dexcom G5 CGM and Medtronic Enlite data are from different studies and are not a head-to-head comparison within one study.

Figure 3: Percentage of Dexcom G5 CGM (Dexcom) and Medtronic Enlite sensor (Medtronic) readings that are within ±15 mg/dL of the reference laboratory analyzer (for sensor readings less than 80 mg/dL), or within ±20% of the reference laboratory analyzer (for sensor readings greater than 80 mg/dL).

CGM-Reference Concurrence in various Glucose concentration ranges		
	Dexcom	**Medtronic**
40-60 mg/dL	89%	75%
61-80 mg/dL	91%	77%
81-180 mg/dL	92%	70%
181-300 mg/dL	93%	83%
301-350 mg/dL	94%	90%
351-400 mg/dL	92%	87%

Low Glucose Detection Rate:
Since CGMs evaluate users' glucose levels continuously, and in real time, they allow for alarms and configurable alerts. The G5 CGM has a fixed alarm at 55 mg/dL to warn users when their system glucose reading is below 55 mg/dL (this alarm cannot be disabled by the user). In addition to this alarm, users can set alerts, which serve the same purpose as alarms but can be customized (i.e., between 55 and 100 mg/dL) to provide users with an earlier warning that their blood glucose is falling (e.g., users often choose 80 mg/dL as a complimentary alert to the fixed 55 mg/dL alarm). Dexcom evaluated how well the G5 CGM performed with regard to these alerts and alarms, using their sensor accuracy study data. The system was blinded to the user during the study, so alerts and alarms were analyzed retrospectively by comparing the glucose value obtained using the reference laboratory analyzer (as "truth") to the time it took for the G5 CGM to register a glucose value at or below the alert/alarm setting.

The Low Glucose Detection Rate (see Figure 4 below: "Detection Rate") is the rate that the device alerted when it should have alerted (i.e., the rate at which the device sounds an alert when blood glucose is below the low glucose alert threshold). The Missed Detection Rate as the rate at which the device did not alert when it should have (i.e., the rate at which blood glucose was below the low glucose alert threshold and the device did not sound an alert). For example, per the table below, for adults, the G5 CGM alerted 91% of the time when the subjects had glucose less than 70 mg/dL, but only 83% of the time when the subjects' glucose fell below 60 mg/dL. (Note that ages 6 and up were compared to a laboratory reference analyzer and ages 2-5 were compared to SMBG). Missed detection rates are important in hypoglycemic conditions because it is important that users be notified when their blood sugar is low so that they can correct the low blood sugar. A low missed detection rate indicates that users can have confidence that they will be notified by the device if their blood sugar is low.

Figure 4: The Hypoglycemia Detection Rate and Missed Detection Rate for various alert thresholds.

Hypoglycemic Alert Level	55 mg/dL		60 mg/dL		70 mg/dL		80 mg/dL		90 mg/dL	
Population	*Pediatric*	*Adult*	*Pediatric*	*Adult*	*Pediatric*	*Adult*	*Pediatric*	*Adult*	*Pediatric*	*Adult*
Detection Rate	75	68	78	83	75	91	91	90	93	94
Missed Detection Rate	25	32	23	17	25	9	9	10	7	6

High Glucose Alert Rate:

Likewise, users can set G5 CGM alerts to indicate when blood glucose rises to high set thresholds. The High Glucose False Alert Rate (see Figure 5 below) is the rate that the alarm incorrectly alerted when the users' glucose was actually below the high threshold but the CGM detected that it was above the threshold, out of all of the times it alerted. For example, per the table below, for pediatrics, the G5 CGM high glucose alerts would have incorrectly indicated that the subject was above the high glucose alert threshold 20% of the time when the subjects had glucose greater than 240mg/dL, and 13% of the time when the subjects rose above 180mg/dL. (Note that ages 6 and up were compared to a laboratory reference analyzer and ages 2-5 were compared to SMBG). False alert rates are important in hyperglycemic conditions because if a user is falsely notified that their blood sugar is high, they might treat themselves based on this false high result inappropriately. A low false alert rate gives a user confidence that the glucose values in the hyperglycemic range are likely to be accurate most of the time.

Figure 5: The Hyperglycemia False Alert Rate for various alert thresholds.

Hyperglycemic Alert Level	120 mg/dL		180 mg/dL		220 mg/dL		240 mg/dL		300 mg/dL	
Population	*Pediatric*	*Adult*	*Pediatric*	*Adult*	*Pediatric*	*Adult*	*Pediatric*	*Adult*	*Pediatric*	*Adult*
False alert Rate	8	2	13	3	19	6	20	7	29	14

ii.   Monte Carlo-based In silico simulations

As stated above, Dexcom conducted *in silico* simulations that were intended to model the performance of the G5 CGM, including considering the impact of certain variables (within the broad categories of device, physiological, and behavioral variables) on safety-related outcomes. The *in silico* experiments were primarily designed to assess the safety of pre-meal insulin dosing using CGM versus SMBG (one simulation also assessed hyperglycemia correction without a meal).

How does the model work?

Dexcom's model was based on the Monte Carlo method. This method allows for simultaneous or individual manipulation of multiple variables that may then be fed into equations to calculate insulin dosing and to calculate final glucose concentrations. These

variables can be confined to particular maximum and minimum ranges, and their distribution can be controlled (e.g., random distribution vs. Gaussian).

Each *in silico* experiment was performed using 50,000 simulated "subjects." Each "subject" was randomly assigned:
- a "true" pre-meal blood glucose value,
- a "true" pre-meal glucose rate of change (ROC),
- a specific insulin sensitivity, and
- a "true" carbohydrate (CHO) content for their meal.

Each subject was also given:
- a "measured" pre-meal SMBG value,
- a "measured" pre-meal CGM value with trend arrow, and
- an "estimated" meal CHO content (with error).

The error in the "measured" SMBG and CGM values was modeled based on Dexcom's observed SMBG and CGM data from the clinical study described in Section V(a) above.

Pre-meal insulin dosing was calculated using the following equation (a modified version of the DirecNet Applied Treatment Algorithm).[3]

$$dose = \left(\frac{gluc_{meas} - gluc_{target}}{ISF} + \frac{CHO}{I:C} \right) \cdot IAF$$

In this equation:
- $gluc_{meas}$ is the pre-meal glucose level- either the "true" glucose level assigned, or the level
- $gluc_{target}$ is always 100 mg/dL (the target glucose goal following the meal)
- *CHO* is the subject's meal carbohydrate content – either the "true" CHO content assigned, or the "estimated" CHO content,
- ISF is the assigned insulin sensitivity factor for the "subject,"
- I:C is the "subject's" insulin to CHO ratio, and
- *IAF* is the insulin adjustment factor based on the pre-meal glucose ROC – either the "actual" ROC assigned, or the "measured" trend on the CGM.

For SMBG *in silico* dosing, IAF in the model was set to equal 1 (i.e., no dose adjustment based on glucose rate of change), since SMBG does not provide trend information. For CGM trend "measurement", IAF was set according to the simulated glucose trend arrow on the "measured" CGM, as described below in Figure 6[5].

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[5] The insulin adjustment factor was based on findings from the DirecNet group; see Appendix 2: Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator).

Figure 6: Insulin Adjustment Factor settings according to the simulated glucose trend arrow on the CGM.

Simulated CGM "Measured" Pre-prandial ROC	Trend Arrow on CGM Display		Insulin Adjustment Factor (IAF)
ROC ≥ 3	Double arrow up	⬆⬆	1.3
$2 \leq$ ROC < 3	Single arrow up	⬆	1.2
$1 \leq$ ROC < 2	45° arrow up	⬈	1.1
$-1 <$ ROC < 1	Flat arrow	➡	1
$-2 <$ ROC ≤ -1	45° arrow down	⬊	0.9
$-3 <$ ROC ≤ -2	Single arrow down	⬇	0.8
ROC ≤ -3	Double arrow down	⬇⬇	0.7

Insulin dosing was calculated three times for each simulated subject:

1. "optimal" dose using the true pre-meal glucose value, the true pre-meal ROC, and the true CHO content of the meal,
2. "actual" SMBG dose using the "measured" pre-meal glucose value by SMBG (with associated modeled error), an IAF of 1 (because no ROC information is available for SMBG), and the "estimated" CHO content of the meal, and
3. "actual" CGM dose using the "measured" pre-meal glucose value by CGM (with associated modeled error), an IAF based on the simulated trend arrow, and the "estimated" CHO content of the meal.

For example, an in silico "subject" may have the following "optimal" and "actual" doses that would be modeled in this simulation using the dosing algorithm (also listed above; where the "optimal" dose represents the dose calculated when all dosing variable are precisely known, and the "actual" dose represents the dose calculated when model variables are incorporated (e.g. meal carbohydrate counting errors, CGM inaccuracy, etc.):

$$dose = \left(\frac{gluc_{meas} - gluc_{target}}{ISF} + \frac{CHO}{I:C} \right) \cdot IAF$$

EXAMPLE:	"Optimal" (true)	"Actual" SMBG	"Actual" CGM
Pre-Meal Glucose	185, ROC 1.2	197	203, single arrow up
IAF	1.1	"1"	1.2
Glucose target	100	100	100
CHO	16 g	14 g	14 g
ISF	45	45	45
I:C	11.25	11.25	11.25
Insulin Dose	**3.61 U**	**3.40 U**	**4.24 U**

These simulated "optimal" and "actual" insulin doses were then used to estimate the risk of hypoglycemia or hyperglycemia for each subject and scenario by calculating the predicted post-meal (post-dose) glucose level using the following equation.

$$gluc_{post} = gluc_{target} - ISF \ (dose_{actual} - dose_{optimal})$$

Hypoglycemia was defined as a calculated post-meal glucose level of <70 mg/dL. Hyperglycemia was defined as a calculated post-meal glucose level of >180 mg/dL. Therefore, if we continue the example above, the following post-meal glucose levels would be predicted for this hypothetical subject:

"Optimal" (true)	"Actual" SMBG	"Actual" CGM
100 mg/dL	109.5 mg/dL	71.7 mg/dL

The differences between these simulated scenarios were then compared and are the basis of the "SMBG" and "CGM" data in the graphs below on pages 19-24.

In addition, Dexcom created a separate model to assess the likelihood that the CGM low glucose alert may occur. The starting point for each subject in this simulation was the predicted post-meal glucose value ("true" value) following the CHO meal in the above experiment for each subject (i.e., the starting glucose level was the only input that varied). Dexcom then applied a model of CGM measurement and a fixed -1 mg/dL/min ROC. They compared the point at which the modeled CGM value crossed the 70 mg/dL alert threshold compared to a "perfect" -1 mg/dL/min decrease in glucose value (see Figure 7 below; Dexcom used the -1 mg/dL/min ROC because that was the average ROC observed in non-interventional Dexcom clinical studies).

Figure 7: Schematic depicting alert assessment in the Monte Carlo simulations.
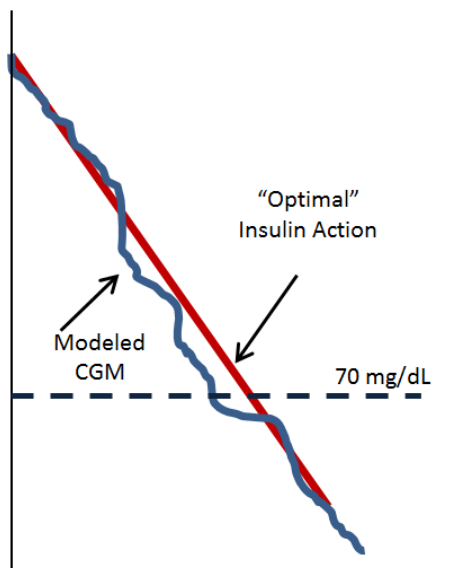
The number of post-meal hypoglycemic events that could potentially be mitigated by Dexcom G5 alerts was determined as follows: If an alert was predicted to occur within ± 15 minutes of the time that the actual glucose crossed 70 mg/dL, the alert was considered a mitigation to the risk of hypoglycemia. That is, if the modeled CGM value reached the threshold (70 mg/dL) within +/- 15 minutes of the "perfect" glucose trajectory, Dexcom considered the alert successful. Dexcom determined that successful alerts adequately mitigate the risk of hypoglycemia. In the graphs below on pages 19-24 for the "CGM with low glucose alert" condition, hypoglycemic risk was modeled with a user adjustable alert threshold set for a CGM value of 70 mg/dL; in the "CGM" condition, risk was modeled using the fixed Dexcom CGM alarm threshold of 55 mg/dL.

The following is an example of a graph of the modeled "SMBG," "CGM," and "CGM with low glucose alerts." In this example, the X axis is varying pre-meal ROC and the Y axis is frequency of post-meal glucose below 70 mg/dL.
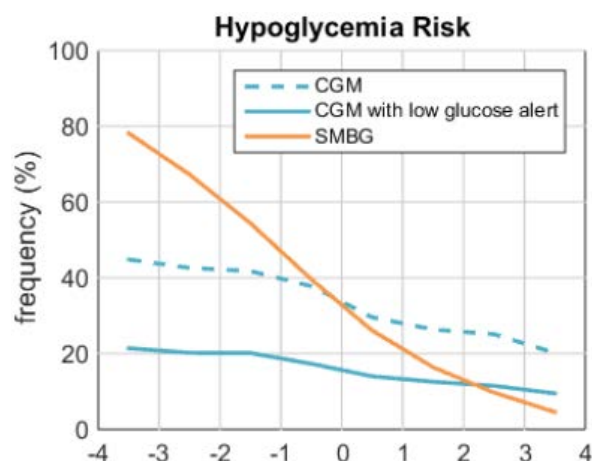
Simulation Results

Figures 8-15 are selected results of the simulations described above. For the full report and a description of all simulations performed, see Appendix 1.

Figure 8: Simulated frequency of post-meal glucose <70 mg/dL ("hypoglycemia risk") and post-meal glucose >180 mg/dL ("hyperglycemia risk") all simulated subjects.
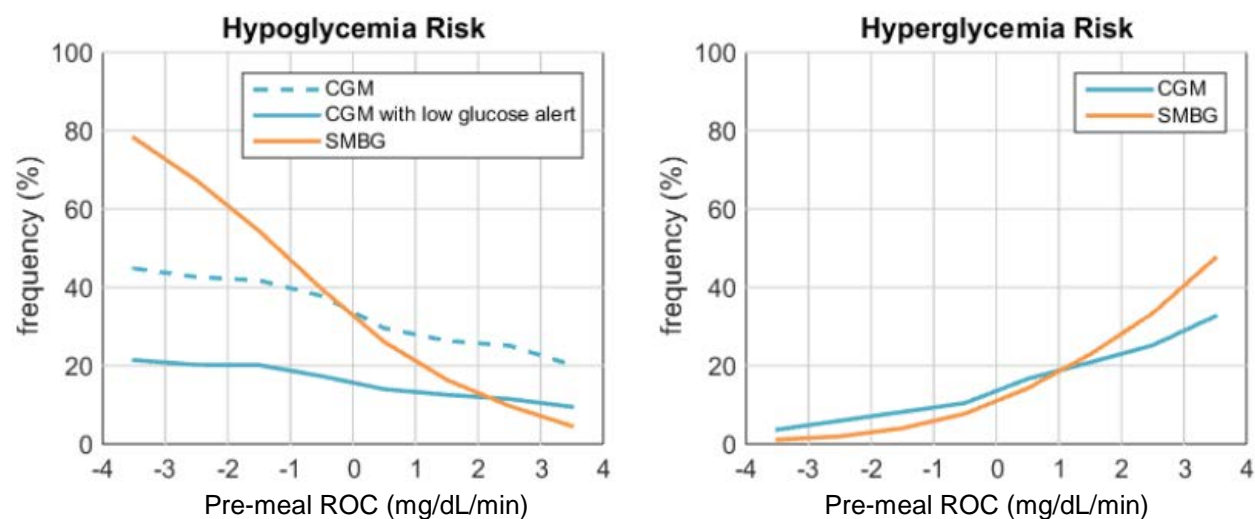
Figure 9: Simulated frequency of post-meal glucose <70 mg/dL ("hypoglycemia risk") and post-meal glucose >180 mg/dL ("hyperglycemia risk") for Adult subjects compared to Pediatric subjects (the light blue dashed and solid lines are there for comparison, and are the "CGM" and "CGM with low glucose alert" simulations for the full population, respectively).
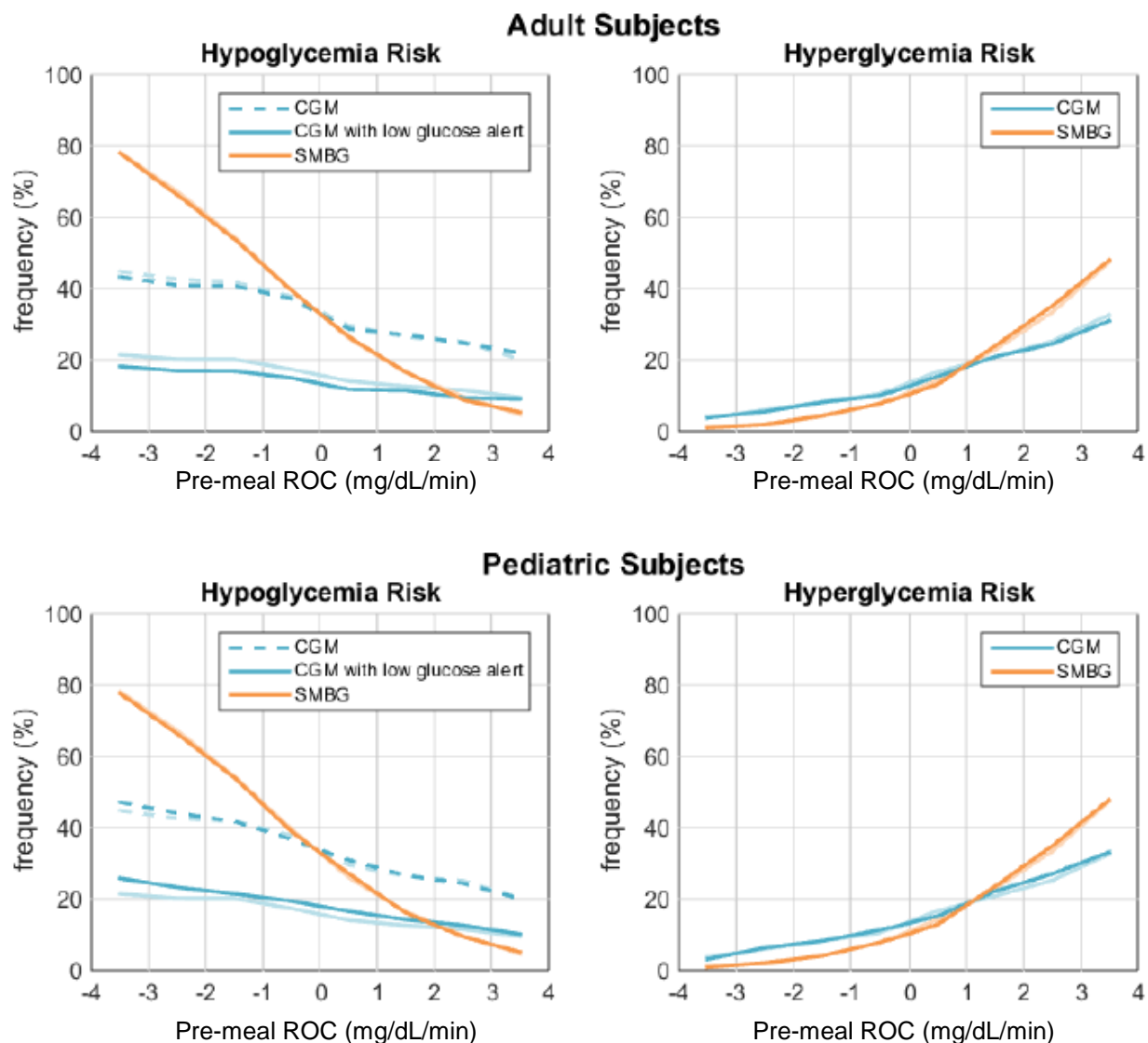
Figure 10: Simulated frequency of post-meal glucose <70 mg/dL when alert threshold is set to 55 mg/dL (the light blue line is there for comparison and is the "CGM with low glucose alert" simulation when the alert is set to 70 mg/dL).

Figure 11: Simulated frequency of post-meal glucose <70 mg/dL ("hypoglycemia risk") and post-meal glucose >180 mg/dL ("hyperglycemia risk") when trend information is not considered in calculating "actual" insulin dose (dark blue dashed and solid lines; the light blue dashed and solid lines are there for comparison, and are the "CGM" and "CGM with low glucose alert" simulations with trend information used, respectively).
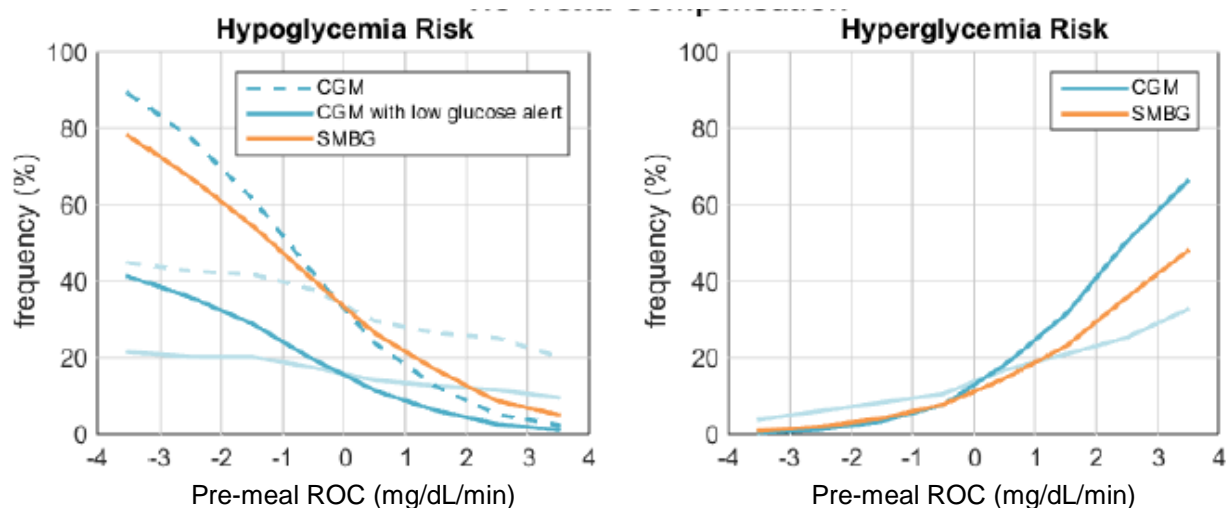
Figure 12: Simulated risk of post-meal glucose <70 mg/dL ("hypoglycemia risk") and post-meal glucose >180 mg/dL ("hyperglycemia risk") when trend compensation (ROC) is doubled when calculating "actual" insulin dose (dark blue dashed and solid lines; the light blue dashed and solid lines are there for comparison, and are the "CGM" and "CGM with low glucose alert" simulations with correct trend information used, respectively).
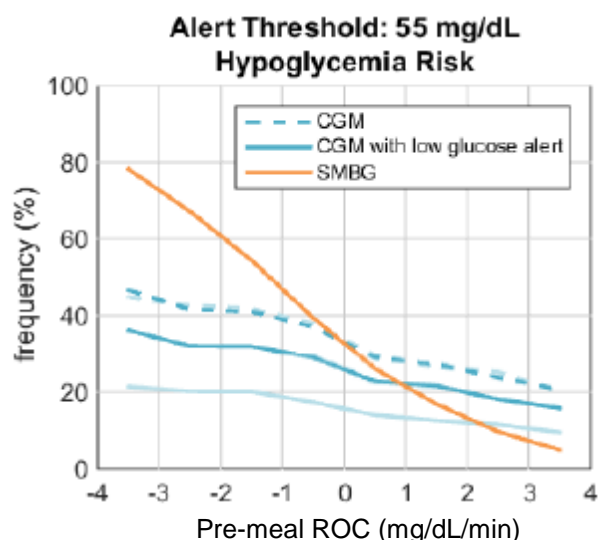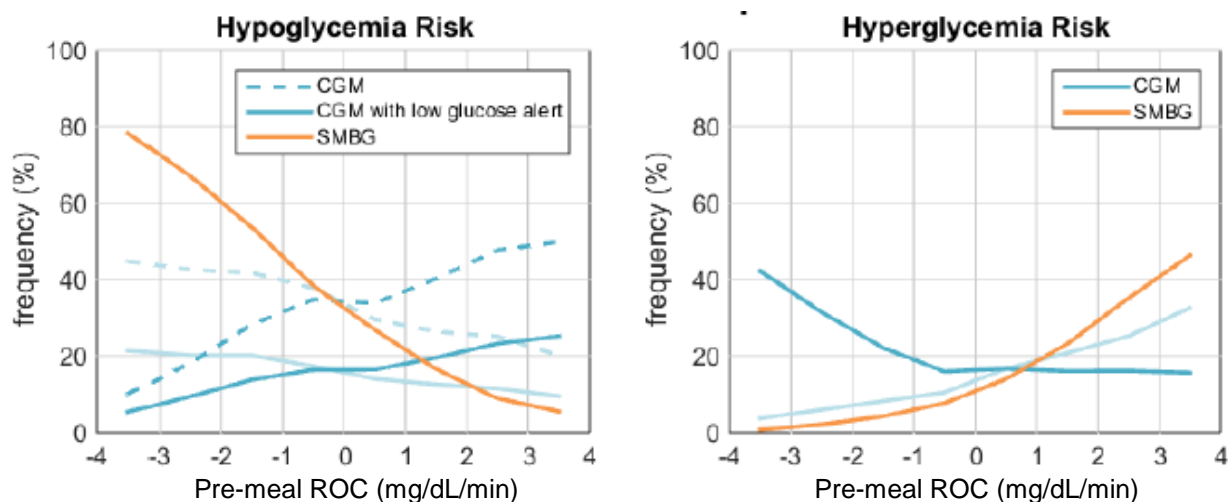

Figure 13: Simulated risk of post-meal glucose <70 mg/dL ("hypoglycemia risk") and post-meal glucose >180 mg/dL ("hyperglycemia risk") when varying ROC errors occur when calculating "actual" insulin dose. A histogram of the observed occurrence of ROC change errors in the sensor accuracy clinical trial is included for reference.
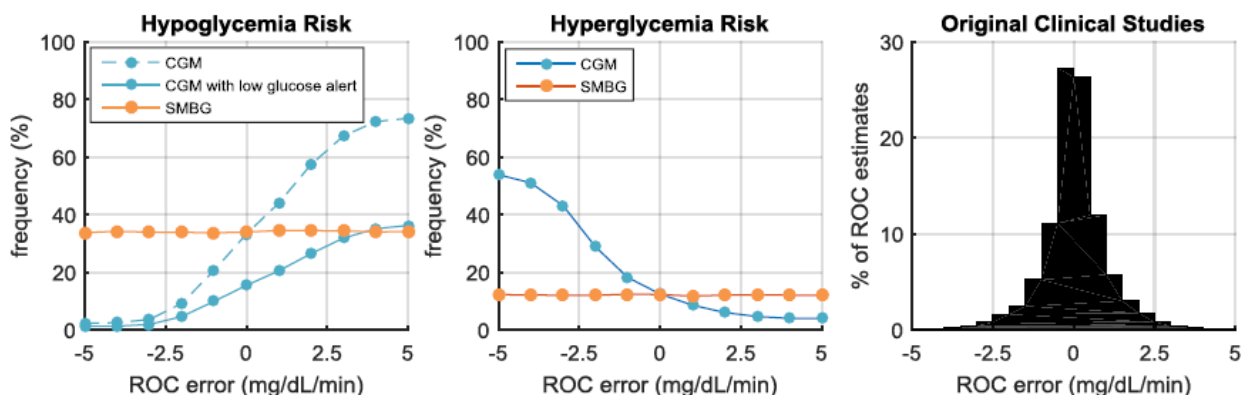
Figure 14: Simulated frequency of post-meal glucose <70 mg/dL for individual simulated sensors (based on sensor performance during the sensor accuracy study). For each simulated sensor, a set of 50,000 subjects were simulated, and the resulting frequency of hypoglycemia from "SMBG" (orange), "CGM" (open blue), and "CGM with low glucose alert" (blue) are shown as individual circles. The same SMBG error model was used for each simulation; variation in SMBG risk is due only to random variation between simulations.
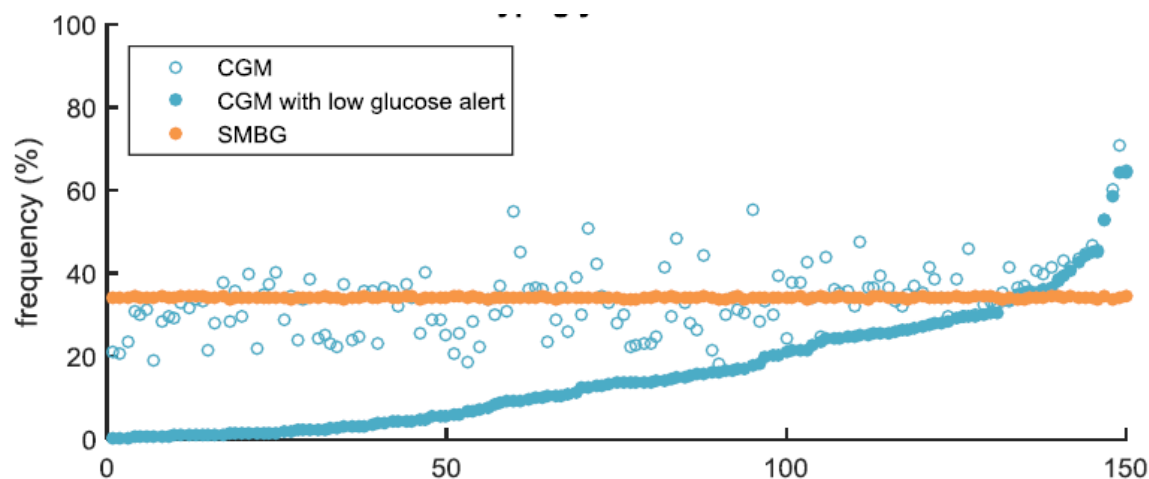
Figure 15: One simulation did not assess mealtime dosing, and looked at hyperglycemia correction dosing. Simulated risk of glucose <70 mg/dL ("hypoglycemia risk") and glucose >180 mg/dL ("hyperglycemia risk") when calculating a correction dose are shown.
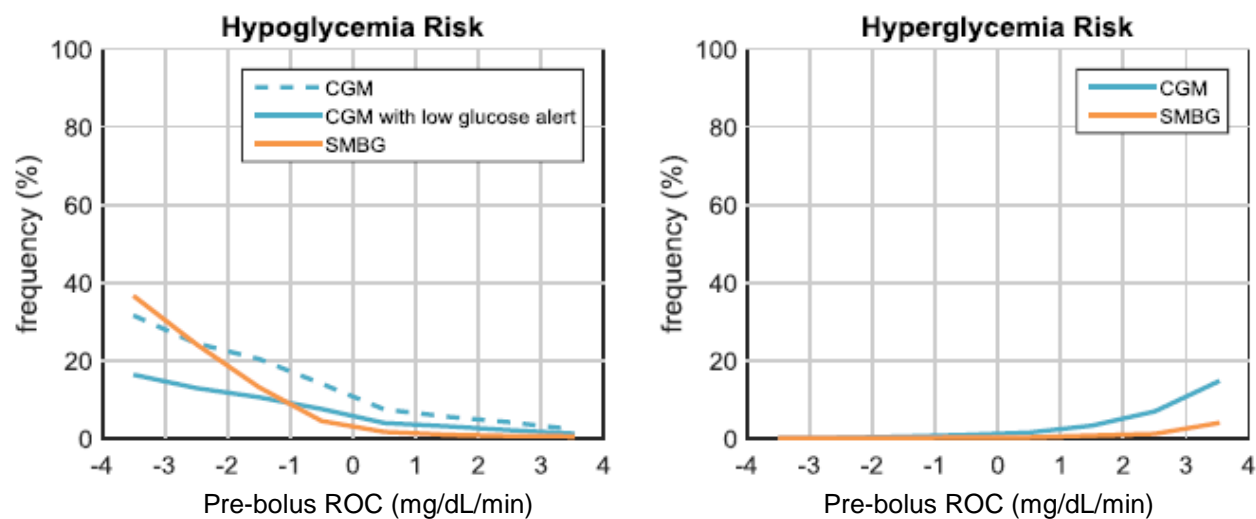
Discussion

One potential limitation of the Monte Carlo modeling is that, with the exception of the scenario where users made incorrect dosing decisions based on the trend arrow, Dexcom

did not stress the simulations to the point where, in each scenario, Dexcom concluded that use of the CGM to calculate insulin doses may not be safe. Thus, the simulations allow for only a qualitative interpretation of the safety of non-adjunctive use of the G5 CGM. Another limitation of the Monte Carlo simulation model, which is a custom-generated model by Dexcom, is that the model was not independently validated. Some independent validation of the model assumptions and construction, and a more comprehensive stressing of the simulation scenarios to identify where non-adjunctive use of the Dexcom G5 would not be safe may be helpful. The following are some additional potential Model Assumptions/Limitations:

- The dosing simulation did not involve a physiological model, so only a few parameters were randomly varied for each *in silico* "subject": pre-meal glucose value, pre-meal glucose rate of change, insulin sensitivity, and carbohydrates consumed.
- All SMBG simulations assumed the subject would dose as if there was no ROC. In practice, some people with diabetes will have some knowledge of glucose ROC (including those already using CGM adjunctively).
- All subjects basing decisions on SMBG measurements were assumed to not perform post-meal glucose tests (had no mitigation for post-meal hypoglycemia).
- Subjects did not learn from their experience.
- Subjects did not have symptoms of hypoglycemia.
- There was no error in a subject's estimation of their insulin sensitivity factor or insulin-to-carbohydrate ratio in the baseline simulation (except in scenarios where ranges were varied).
- Insulin dose adjustment using trend arrows was standardized in this simulation in a manner that may not be well understood in the diabetes community (In additional scenarios, Dexcom tested the impact of not using trend information or making errors in trend adjustments).
- Although the default and most commonly used low threshold alert setting is 80 mg/dl, simulations that included a CGM low glucose alert had that alert set to a threshold of 70 mg/dL (except in one scenario when alert settings were varied). No hyperglycemia alerts were simulated for CGM.
- The low glucose alert simulation used a glucose rate of change of -1 mg/dL/min for all patients regardless of other factors, including the glucose rate of change at the time of dosing (except in scenarios where this rate of change was varied).
- Dexcom provided limited presentation of the results (e.g., post-meal glucose <70 mg/dL per pre-meal ROC). Additional analyses may be helpful.

iii.   *In silico experiment using the UVA-Padova T1DM simulator*

To provide additional support for the non-adjunctive intended use of their device, Dexcom used a computer model to conduct an *in silico* clinical trial (ISCT) comparing acute safety outcomes in virtual subjects using either non-adjunctive CGM, or SMBG. To do this, Dexcom used a computer model to conduct an ISCT trial that differs from the Monte Carlo simulations described above. The ISCT used individual virtual subjects created using

experimentally-derived physiological data. Based on these data, the physiological parameters assigned to these subjects span the observed inter-individual variability of key diabetes-related metabolic parameters in the general population of patients with Type I diabetes[6,7,8]. These subjects were then assigned simulated behaviors related to diabetes management and assessed for incidence and rate of hypoglycemia, hyperglycemia, and euglycemia over a two week period.

Background and summary of modeling conditions and parameters

The virtual subjects of this ISCT exist within the UVA-Padova T1DM simulator[8,10]. As of 2014, this simulator has been used by 32 academic research groups, and results of the simulator presented in 63 peer-reviewed publications. This simulator has also been accepted by FDA as a substitute for preclinical trials of certain diabetes treatments. The simulator contains 300 distinct virtual subjects: 100 adult, 100 adolescent and 100 pediatric. These subjects are described by 36 physiological parameters which are derived from experimental studies of healthy human physiology and glucose/insulin/carbohydrate metabolism[8]. The parameters have been modified to account for alterations in glucose metabolism produced by Type 1 diabetes, including based on recent data related to counter-regulatory effects and experimentally determined circadian-rhythm dependent changes in insulin sensitivity[10]. Each virtual subject has a unique combination of values of the 35 different model physiological parameters. Available values of these parameters for the adult, adolescent and pediatric subjects are set to represent the expected ranges in those specific populations. Each virtual subject therefore represents a unique physiological profile related to glucose control.

Virtual subjects were studied in four patient cohorts representing four distinct populations: adults with mixed hypoglycemia awareness, adults with impaired hypoglycemia awareness, pediatrics with mixed hypoglycemia awareness and pediatrics with impaired hypoglycemia awareness. Mixed hypoglycemia awareness and impaired hypoglycemia awareness indicate the glucose levels at which subjects were assumed to recognize and respond to symptoms of hypoglycemia. Cohorts with mixed hypoglycemia awareness were defined as 80% of subjects recognizing hypoglycemia symptoms at BG levels of 55-70 mg/dl and 20% recognizing symptoms at 40-55 mg/dl. In the impaired hypoglycemia awareness cohorts, all the virtual patients recognized hypoglycemia symptoms at 40-55 mg/dl.

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[6] Kovatchev B.P., Breton M., Man C.D., and Cobelli C. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. *J Diabetes Sci Technol.* 2009. Jan; 3(1): 44-55.

[7] Appendix 3: Dexcom RPT-904020, Rev 001: Non-Adjunctive Use of CGM: In Silico Clinical Trial With the Uva/Padova T1d Simulator.

[8] Man, C.D., Micheletto, F., Lv, D., Breton, M., Kovatchev, B., Cobelli, C. The UVA/PADOVA Type 1 Diabetes Simulator: New Features. *J Diabetes Sci Technol.* 2014. Jan 1; 8(1): 26-34.

Each of the 100 virtual subjects was then assigned a set of behavioral parameters intended to span the range of typical diabetes management behaviors. These behaviors included carbohydrate-counting errors, postprandial test frequency, CGM alert threshold, SMBG test frequencies, meal sizes and times, and subject-specific thresholds for recognition of hypoglycemia symptoms; parameters for each behavior were randomly assigned to each subject. The range and distribution of possible values for each behavioral parameter was based on Dexcom medical staff's clinical experience and judgment, published information on behavior of people with Type 1 diabetes, and actual use data available to Dexcom in their technical support repository. Two general examples of how the range of values of these behavioral parameters was derived are provided below:

- In the SMBG arm, the number of post-meal blood glucose tests performed per day was distributed according to published data regarding testing frequency in patients with Type 1 Diabetes;

- In the CGM arm, the distribution of low glucose alert thresholds was set to mimic the actual distribution of these alerts used by current Dexcom users based on data users have chosen to share with Dexcom.

Assignment of behavioral parameters was repeated 100 times for each subject to allow each specific subject physiology to be assigned a wide variety of behaviors and allow for the modeling of specific patient physiologies under a wide variety of behavioral conditions. This resulted in a total of 10,000 simulated physiology-behavior combinations (or virtual subject behaviors, VSBs) analyzed through a 2-week treatment period, for each of the 4 cohorts.

As stated above, the distribution of low glucose alert thresholds in this ISCT was set to mimic the distribution of these alerts used by current Dexcom users based on data users have chosen to share with Dexcom. Based on this field data, 26% of VSBs used a low threshold alert of 70 mg/dL, 60% of VSBs used 80 mg/dL, and 14% of VSBs used no manual alerts and only used the 55 mg/dL alarm. Note that in Dexcom's Monte Carlo based simulations, there was generally an overall increase in modeled hypoglycemia risk when CGM with no alerts was used compared to when SMBG was used. However, only 14% of the simulations in this ISCT assessed that use case.

Simulation conditions

For each day of the simulation, each VSB was modeled as consuming three meals per day (between 06:30 am and 08:00 am for breakfast, 11:30 am and 01:00 pm for lunch, 06:30 pm and 08:00 pm for dinner). Different carbohydrate ranges for each meal were used for pediatric and adult subjects. Within the pediatric population, different carbohydrate ranges for each meal were used for VSBs aged <4 years, between 5 and 7 years, and >8 years old. CGM sensor calibrations (using SMBG measurements) were performed at 06:00 am and

06:00 pm. VSBs in the in silico clinical trial were faced with 3 different diabetes management scenarios including (i) daily meals involving pre-meal insulin boluses, (ii) correction boluses in response to CGM values, CGM alerts, or elevated post-prandial BG levels measured by SMBG, and (iii) treatment of low glucose with carbohydrates in response to CGM alerts and/or hypoglycemia symptoms.

In response to the specific diabetes management scenarios (meals, hypoglycemia, and hyperglycemia) the VSBs made treatment decisions according to available information and treatment rules imposed by the simulation. Treatment rules for hypoglycemia and hyperglycemia were based on Dexcom medical staff's clinical experience and common clinical practice:

When SMBG-based treatment was simulated:

- pre-meal insulin boluses were calculated based on the patient's estimate of meal carbohydrate content and a correction component based on SMBG;

- insulin correction boluses to correct hyperglycemia were generated and calculated according to SMBG in response to routine post-meal tests in a subset of virtual patients (Dexcom assumed that not all patients using SMBG would regularly conduct post-meal tests), and pre-sleep tests in all;

- hypoglycemia treatments were generated in response to recognition of hypoglycemic symptoms.

With non-adjunctive CGM-based treatment:

- pre-meal insulin boluses were calculated based on the patient's estimate of meal carbohydrate content and a correction component based on the CGM glucose reading and trend arrow[9]. Briefly, for a 1-2 mg/dL/min trend arrow the bolus calculation would add (upward trend) or subtract (downward trend) 25mg/dL from the input concentration glucose used in the dosing equation. For a 2 or 3 mg/dL/min trend arrow the bolus calculation would add (upward trend) or subtract (downward trend) 50 mg/dL from the input glucose concentration used in the dosing equation.

- post-meal and pre-sleep correction boluses were generated in response to routine post-meal and pre-sleep checks and CGM high glucose alerts and calculated according to CGM glucose reading and trend arrow;

- hypoglycemia treatments were generated in response to CGM low glucose alerts or alarms or in response to hypoglycemic symptoms.

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[9] Scheiner, G. Hone In On The Range. Diabetes Self Manag. 2015. Jul-Aug; 32(4): 18-20, 23.

CGM performance in the ISCT was modeled from the data collected in the clinical studies to determine CGM accuracy in adult and pediatric subjects described above. Each day of sensor life was modeled separately to reflect known differences in CGM performance over sensor life. Glucose meter performance in the ISCT was modeled from clinical trial data collected by Dexcom using the Bayer Contour Next blood glucose meter during their clinical study of adults performed to support approval of the Dexcom G5 system.

Analysis of the simulations

Results for each cohort (adult and pediatric, mixed hypoglycemia awareness and hypoglycemia unware) were collected and the following primary outcome metrics were calculated:

- average time and number of events below 50 mg/dl

- average time and number of events below 70 mg/dl

- average time between 70 mg/dl and 180 mg/dl

- average time above 180 mg/dl

- average time above 250 mg/dl

These metrics were compared between CGM-based treatment and SMBG-based treatment across each full seven day sensor wear period. In addition, because CGM performance on day 1 of sensor wear is known to be worse than performance on days 2-7, Dexcom also analyzed and reported outcomes based specifically on performance of their CGM on day 1 of sensor wear separately from days 1-7 combined. Importantly, because the data were simulated, the "true" glucose values of each subject were known at all times and could be used to calculate the outcome metrics.

Selected Results

The full report of this simulation is included in Appendix 3. A summary of the results are below. Figures 16-18 summarize the results of CGM performance modeled across all days of sensor wear (i.e., days 1-7).

Figure 16: Modeled Rate of Hypoglycemic events in Adults and Pediatrics

			Mixed hypoglycemia awareness		Impaired hypoglycemia awareness	
			SMBG	**CGM**	**SMBG**	**CGM**
Adult	Events below 50 mg/dl	Rate* [per VSB-week]	0.57	0.46	1.58	0.95
		Event duration [min] (±SD)	25.94 (±16.99)	21.85 (±11.50)	31.86 (±19.91)	24.64 (±12.52)
	Events below 70 mg/dl	Rate [per VSB-week]	2.99	3.01	2.93	2.97
		Event duration [min] (±SD)	58.03 (±36.58)	44.74 (±23.81)	93.76 (±51.61)	58.37 (±33.38)
Pediatric	Events below 50 mg/dl	Rate [per VSB-week]	0.24	0.23	0.83	0.47
		Event duration [min] (±SD)	26.94 (±20.56)	20.03 (±11.84)	31.24 (±22.64)	22.01 (±13.01)
	Events below 70 mg/dl	Rate [per VSB-week]	1.99	2.03	1.95	1.99
		Event duration [min] (±SD)	54.40 (±37.95)	40.53 (±25.07)	92.13 (±52.3)	51.72 (±32.77)

*Event rate is the average rate of the event observed across all 10,000 VSBs in each simulated population. For example, a rate of 0.46 events below 50mg/dL per VSB-week means that, on average, a VSB in the simulation experienced 1 event below 50mg/dL approximately every two weeks.

Figure 17: Modeled Time in Ranges in Adults

Adults

		Mixed awareness population		Impaired awareness population	
		SMBG	**CGM**	**SMBG**	**CGM**
Time below 70 mg/dL	Median [min/day]	19.14	14.93	34.29	20.36
	IQ range *[min/day]	[7.00 – 35.64]	[5.00 – 28.50]	[11.86 – 58.64]	[6.57 – 37.63]
Time 70-180 mg/dL	Median [hours/day]	15.76	16.23	15.60	16.18
	IQ range [hours/day]	[13.84 – 18.07]	[14.37 – 18.33]	[13.71 – 17.85]	[14.32 – 18.26]
Time above 180 mg/dL	Median [hours/day]	7.93	7.53	7.90	7.52
	IQ range [hours/day]	[5.50 – 9.82]	[5.31 – 9.38]	[5.46 – 9.71]	[5.30 – 9.34]
Time above 250 mg/dL	Median [min/day]	125.57	119.07	125.21	118.21
	IQ range [min/day]	[62.64 – 211.84]	[59.71 – 197.86]	[62.29 – 212.11]	[59.73 – 198.20]

*IQ range is the InterQuartile range; the range of values between which 50 percent of the data points are found (from the 25th percentile to 75th percentile).

Figure 18: Modeled Time in Ranges in Pediatrics

Pediatrics		Mixed awareness population		Impaired awareness population	
		SMBG	**CGM***	**SMBG**	**CGM**
Time below 70 mg/dL	Median [min/day]	11.14	8.71	20.57	11.36
	IQ range *[min/day]	[3.80 – 21.43]	[3.43 – 16.36]	[7.36 – 37.77]	[4.43 – 21.00]
Time 70-180 mg/dL	Median [hours/day]	14.05	14.28	13.99	14.28
	IQ range [hours/day]	[11.96–16.35]	[12.26–16.50]	[11.90–16.24]	[12.24–16.50]
Time above 180 mg/dL	Median [hours/day]	9.73	9.54	9.64	9.51
	IQ range [hours/day]	[7.32–11.88]	[7.28–11.58]	[7.22–11.80]	[7.21–11.56]
Time above 250 mg/dL	Median [min/day]	212.64	200.21	212.07	200.57
	IQ range [min/day]	[116.93–330.77]	[112.40–309.55]	[116.30–329.64]	[112.71–309.34]

*IQ range is the InterQuartile range; the range of values between which 50 percent of the data points are found (from the 25th percentile to 75th percentile).

Based on the Monte Carlo simulations described above, low glucose alerts may function within these models to mitigate the predicted risks of hypoglycemia. Figures 19-21 summarize the results of CGM performance modeled across all days of sensor wear (i.e., days 1-7) for the 14% of the *in silico* population that .did not have alerts activated.

Figure 19: Modeled Rate of Hypoglycemic events in Adults and Pediatrics

			Mixed hypoglycemia awareness		Impaired hypoglycemia awareness	
			SMBG	**CGM**	**SMBG**	**CGM**
Adult **No alerts**	Events below 50 mg/dl	Rate* [per VSB-week]	0.57	0.63	1.58	1.54
		Event duration [min] (±SD)	26.84	23.01	31.66	26.42
	Events below 70 mg/dl	Rate [per VSB-week]	3.00	3.49	2.95	3.46
		Event duration [min] (±SD)	58.36	49.32	92.79	67.97
Pediatric **No Alerts**	Events below 50 mg/dl	Rate [per VSB-week]	0.26	0.34	0.81	0.76
		Event duration [min] (±SD)	28.06	21.93	31.39	23.34
	Events below 70 mg/dl	Rate [per VSB-week]	1.98	2.41	1.93	2.35
		Event duration [min] (±SD)	54.72	46.77	90.89	63.01

*Event rate is the average rate of the event observed across the all 10,000 VSBs in each simulated population. For example, a rate of 0.34 events below 50mg/dL per VSB-week means that, on

average, a VSB in the simulation experienced 1 event below 50mg/dL approximately every three weeks.

Figure 20: Modeled Time in Ranges in Adults

Adults (no alerts)		Mixed awareness population		Impaired awareness population	
		SMBG	CGM	SMBG	CGM
Time below 70 mg/dL	Median [min/day]	19.50	19.61	34.29	29.04
	IQ range *[min/day]	[7.36-35.57]	[7.25-37.00]	[11.11-58.71]	[10.64-51.43]
Time 70-180 mg/dL	Median [hours/day]	15.83	16.20	15.63	16.08
	IQ range [hours/day]	[14.12-17.92]	[14.59-18.11]	[13.88-17.73]	[14.42-17.96]
Time above 180 mg/dL	Median [hours/day]	7.86	7.46	7.87	7.46
	IQ range [hours/day]	[5.59-9.57]	[5.38-9.14]	[5.59-9.59]	[5.44-9.14]
Time above 250 mg/dL	Median [min/day]	123.11	116.96	125.00	117.50
	IQ range [min/day]	[64.75-207.00]	[60.00-192.89]	[65.79-207.57]	[62.61-194.75]

*IQ range is the InterQuartile range; the range of values between which 50 percent of the data points are found (from the 25th percentile to 75th percentile).

Figure 21: Modeled Time in Ranges in Pediatrics

Pediatrics (no alerts)		Mixed awareness population		Impaired awareness population	
		SMBG	CGM*	SMBG	CGM
Time below 70 mg/dL	Median [min/day]	11.43	12.04	20.61	16.96
	IQ range *[min/day]	[3.68-21.50]	[5.21-22.00]	[6.64-37.43]	[7.00-31.07]
Time 70-180 mg/dL	Median [hours/day]	14.05	14.35	13.96	14.32
	IQ range [hours/day]	[11.98-16.10]	[12.35-16.38]	[11.92-16.04]	[12.29-16.35]
Time above 180 mg/dL	Median [hours/day]	9.74	9.45	9.61	9.39
	IQ range [hours/day]	[7.61-11.88]	[7.33-11.40]	[7.53-11.85]	[7.24-11.36]
Time above 250 mg/dL	Median [min/day]	224.00	204.61	220.46	204.25
	IQ range [min/day]	[122.14-333.61]	[114.36-308.57]	[121.25-334.04]	[115.00-308.71]

*IQ range is the InterQuartile range; the range of values between which 50 percent of the data points are found (from the 25th percentile to 75th percentile).

Because sensor performance is most variable on day 1 of sensor wear, Dexcom also analyzed the modeled data only on day 1. In the mixed hypoglycemia awareness pediatric population, specifically on day 1 of sensor wear, the incidence of hypoglycemic events below 50 mg/dl was also increased (approximately doubled) for non-adjunctive CGM use relative to the SMBG arm, although the average amount of time spent below 50mg/dL per event was decreased. Dexcom attributed the increase in rate of events less than 50mg/dl in

pediatric subjects on day 1 of sensor wear to the performance of some Dexcom G5 sensors in some pediatric subjects observed in their clinical accuracy study, which translated to excessive meal or correction insulin doses in the simulations (see Figure 22 below).

Figure 22: Modeled Rate of Hypoglycemic events in Adults and Pediatrics on Day 1

			Mixed hypoglycemia awareness		Impaired hypoglycemia awareness	
			SMBG	**CGM***	**SMBG**	**CGM**
Adult	Events below 50 mg/dl	Rate* [per VSB-week]	0.62	0.56	1.62	1.04
		Event duration [min] (±SD)	25.73 (±16.58)	21.46 (±10.24)	31.94 (±20.00)	24.14 (±11.17)
	Events below 70 mg/dl	Rate [per VSB-week]	3.09	3.24	3.02	3.18
		Event duration [min] (±SD)	57.85 (±35.93)	43.40 (±21.08)	92.57 (±51.47)	54.69 (±28.43)
Pediatric	Events below 50 mg/dl	Rate [per VSB-week]	0.29	0.46	0.88	0.89
		Event duration [min] (±SD)	25.76 (±17.58)	21.28 (±11.45)	31.61 (±22.10)	24.41 (±13.01)
	Events below 70 mg/dl	Rate [per VSB-week]	2.02	2.6	1.98	2.56
		Event duration [min] (±SD)	55.58 (±36.92)	42.93 (±25.83)	91.60 (±50.58)	55.75 (±33.37)

*Event rate is the average rate of the event observed across all 10,000 VSBs in each simulated population. For example, a rate of 0.46 events below 50mg/dL per VSB-week means that, on average, a VSB in the simulation experienced 1 event below 50mg/dL approximately every two weeks.

Notably, across all cohorts, the average rate of events below 70mg/dl was slightly increased for non-adjunctive CGM use (especially on day 1 of wear) relative to SMBG. Although the event rate was increased, the average amount of time spent below 70mg/dl was decreased.

Value and Limitations of Dexcom's In Silico Clinical Trial (ISCT):

As for any clinical trial, whether conducted in real or virtual patients, it is important to be aware of the challenges of extrapolating results and outcomes observed in a trial population, given the specific trial conditions, to expected outcomes in actual users. Here we present a summary of some of the values and limitations of this ISCT for consideration by the panel.

There are various advantages to conducting a computer model based comparison rather than conducting a trial in real patients. One advantage is that by using a computer model

each subject can be simultaneously run through multiple treatment conditions, allowing for the exact same set of physiologies and behaviors to be assessed in response to various interventions. In this ISCT, each of the 10,000 virtual subject behaviors (physiology-behavior combinations) per cohort was simultaneously run through two treatment arms: one using SMBG-based treatment decisions and the other using CGM-based treatment decisions. This allows for a much better controlled assessment of outcomes than would be available in real patients because it avoids differences in physiology or behavior that would be seen in parallel arm or cross-over clinical studies. Additionally, use of an ISCT allows for a much greater number of virtual subjects to be studied, and over a wider range of user behaviors and device parameters, than could be studied in an actual clinical trial. This has the potential to result in a broader assessment of performance than would be otherwise available.

However, an ISCT is limited in comparison to a traditional trial in other aspects, in that an ISCT does not incorporate multiple conditions or user behaviors that may be typical of routine diabetes care and could have been observed in a traditional trial. The list of limitations provided below is not meant to be exhaustive, rather it should be taken as providing one set of additional factors that may be considered when interpreting these ISCT results:

- The use of CGM in informing treatment decisions may be different for actual users relative to the simulation conditions. For example, actual CGM users may check CGM values much more frequently (routinely or during periods of hypoglycemia or hyperglycemia) or make different insulin dose adjustments and carbohydrate intake decisions based on trend arrows than allowed in the model; these differences could produce positive or negative potential effects on outcomes;

- The simulation did not include routine daytime or bedtime snacks or snack insulin dosing. This would produce additional glycemic variability that might affect outcomes differentially for non-adjunctive CGM vs. SMBG use;

- The simulation did not include any glycemic contributions of exercise, or any differences in response to exercise that might be seen in non-adjunctive CGM versus SMBG users; for example, a differential treatment approach based on trend information available from CGM and the ease of CGM-based glucose checks vs. SMBG during exercise;

- Virtual subjects differed from real-world users in that the timing of insulin to a meal was not adjusted as is commonly reported by real users; timing of insulin dosing relative to meals might be different between non-adjunctive CGM and SMBG users;

- The model did not account for dosing adjustments based on learning over time; which may lead to context-specific or patient-specific optimization of insulin dosing based on CGM trend information;

- Hypoglycemia unaware individuals were assumed to differ from hypoglycemia aware individuals only in the threshold level at which they would react to hypoglycemic symptoms; however, real hypoglycemia unaware patients may be behaviorally distinct from hypoglycemia aware patients in many ways: for example, they may check their blood glucose more frequently, they may make different treatment decisions at different glucose levels or with different trend information, they may set CGM low glucose alerts at different levels than hypoglycemia aware individuals, etc.;

- Nighttime CGM alerts and recognition of hypoglycemia symptoms were assumed to always wake subjects and result in treatment. This may not be the case in actual patients, and it is possible that CGM alerts and recognition of hypoglycemia symptoms are not equally effective in waking real subjects or prompting treatment.

Non-adjunctive vs. Adjunctive CGM use

The ISCT did not directly conduct a comparison of non-adjunctive CGM use relative to adjunctive CGM use. Given the constraints of the model and the accuracy of SMBG relative to CGM, it is unclear whether adjunctive CGM use would present lower use risks than non-adjunctive use and lead to better outcomes in this ISCT. Benefits of adjunctive use of CGM within the model would depend on how adjunctive use is defined and whether an adjunctive CGM user would be allowed, within the model, to adjust their SMBG-derived insulin dose based on CGM trend information. Further, the manner in which CGM is currently being used adjunctively by actual users is unclear and may include a continuum of use in which users rely on CGM only for alerts, always or only occasionally confirm CGM values with SMBG prior to treatment and never, intermittently, or always adjust treatment based on CGM trend arrows. The model of non-adjunctive CGM use in this ISCT is likely much closer to actual non-adjunctive use (even given the limitations of the model) than a model of adjunctive CGM use might be to actual adjunctive use. Therefore, modeling idealized adjunctive CGM use against non-adjunctive use may be less informative in terms of identifying risks and benefits of non-adjunctive CGM use in actual users than in directly modeling non-adjunctive CGM use relative to the standard of care (SMBG).

iv. *Summary*
FDA seeks the Panel's input on whether the information submitted by Dexcom, including the sensor accuracy study, the Monte Carlo simulations, and the UVA/Padova Simulations, are adequate to support the safety and effectiveness of the G5 CGM to be used non-

adjunctively to replace SMBG measurements for making insulin dosing decisions. This includes the panel's input on the particular *in silico* models used, and whether the assumptions made by Dexcom in generating the models, and the simulations they provided to support this device claim, are sufficient and appropriate. In addition, FDA seeks to better understand whether the information provided is sufficient to understand the expected safety and effectiveness of these devices in a broad population of users, including people with Type I and Type II diabetes, pediatric users, newly diagnosed patients, and other relevant populations.

VI. Human Factors

i. Background

Human factors and usability engineering (human factors), as applied to medical devices, involves understanding how people interact with device technology. A major goal of applying human factors to medical devices is to ensure that devices are designed such that risks to users during device use are minimized or eliminated. Human factors testing is performed to assess whether risks have been successfully addressed by device design.

Understanding human factors related to non-adjunctive CGM use can inform the risks of using CGM this way. Specifically, a major component of non-adjunctive CGM use involves users correctly extracting CGM information and using this to make diabetes treatment decisions; there are various risks associated with this interaction. For example, if a user fails to correctly interpret CGM information, or if a user does not understand when CGM information should and should not be used for making treatment decision, they could make a potentially harmful decision. Human factors studies can be performed to assess whether device use risks have been successfully addressed in the design of the device (including the design of training and labeling).

ii. Dexcom Human Factors Studies

Dexcom conducted multiple human factors studies for the use of the G5 CGM in place of SMBG for making treatment decisions. This testing considered the intended device users (adult, pediatric and adult caregivers), use environment (home use) and the availability of labeling and training. Dexcom performed two initial studies (*formative* usability studies) to evaluate new labeling and training for non-adjunctive G5 CGM use and to assess participants' retention of essential knowledge related to new labeling. These studies were also used to assess whether the labeling or training needed to be changed prior to conducting their first *summative* (larger, more definitive) study[10]. Based on the results of this first summative study Dexcom made further modification to the labeling and training materials which were evaluate in two additional formative studies and a second summative

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[10] Appendix 4: Dexcom Summative Usability Testing - Study Protocol - US

study. Participants in the formative studies had the most difficulty completing the following scenarios, and adults and caregivers had the highest failure rates:

- Updating CGM calibration when the user obtained an inaccurate SMBG value.
- Using CGM values to determine a treatment decision when they do not have trend information (i.e., when there are gaps in CGM data or no trend arrow is present).
- Understanding that CGM calibration should not be performed when the CGM indicates that the glucose level is changing rapidly.

Device labeling, including training materials, tutorial video and getting started guide were modified based on the results of these formative studies. Dexcom then performed a larger study (first summative study) that focused on risk-based scenarios in which CGM was used as a replacement for SMBG glucose testing. Based on results of this first summative study, labeling was further modified and re-assessed in a second summative study. This first summative study enrolled forty-seven (47) participants divided into three user groups to represent the intended use populations, as follows:

- adults aged 18 and above with diabetes, on intensive insulin therapy (n = 16),
- children and adolescents (aged 10-17) who independently manage their diabetes and are on intensive insulin therapy (n =16),
- caregivers who manage diabetes care for children on intensive insulin therapy (n = 15).

Each user group included at least 7 subjects with no CGM experience and at least 7 subjects with CGM experience. Within each group, participants were given one of the following three training options, to simulate the training that is intended to be provided to users:

- one-on-one training with a Dexcom trainer and the getting started guide; or
- self-training using a computer-based interactive training tutorial and the getting started guide; or
- for three participants from each group who are current Dexcom CGM users, there was no formal training in order to mimic users who hear about a change to the indications to allow non-adjunctive use but do not seek any training before using the device this way. Note that for this training option the getting started guide, user guide and computer based interactive training tutorial were available to users but referring to these resources was at the user's discretion.

In the study, each of the 47 participants was individually presented with six scenarios to test their knowledge related to non-adjunctive use of the Dexcom G5 Mobile CGM system. A moderator led users through the scenarios and observed how the users reported they would react in each case. The scenarios were designed to assess "critical" and "essential" tasks related to non-adjunctive CGM use. Critical tasks are those that if not

performed correctly could cause harm to the user; essential tasks are those that are essential to the use of the device.

There were pre-set criteria for success of the critical or essential task for each scenario, and Dexcom evaluated the percentage of users that responded successfully to the different scenarios. In each scenario, users were provided with either a demo receiver or an iPhone with a production equivalent version of the G5 Mobile app; these were used to display specific glucose readings, trends, or simulate relevant events (for example, alarms) that pertained to the training and/or test scenarios. In some scenarios, all users did not successfully complete critical tasks. In these cases, Dexcom determined that failure to complete the task was either acceptable or they re-designed the labeling and training and evaluated these re-designed materials in an additional summative human factors study. The scenarios and outcomes of each scenario from the first summative study—including any further labeling/training revisions and additional human factors testing in the second summative study —are described below. Dexcom's second summative study enrolled similar users and provided similar training options as in the first study. This second study also evaluated additional scenarios related to insulin stacking which were not evaluated in the first summative study.

1. Responding to a Low Glucose Alert (Critical): In this scenario, the receiver or G5 Mobile app was configured to produce a low glucose alarm to assess whether users could acknowledge a low glucose alarm. One hundred percent (100%) of users were successful in performing this task by acknowledging the alarm and there were no use errors.

2. Using CGM Values to Determine a Treatment Decision (Essential): In this scenario, users were told that it had been four hours since lunch, and that they had eaten a snack one hour ago but had forgotten to take insulin for their snack. They were provided with a receiver/phone that showed a glucose value of 208mg/dL and an upwards trend arrow (reflecting a glucose rate of change of +2mg/dL/min). This scenario was designed to assess whether users could recognize a situation in which information being provided by the CGM could be used to make a treatment decision. One hundred percent (100%) of users were successful in performing this task by indicating that they could use the information on the display to determine diabetes treatment decisions. This scenario was re-assessed in a second summative study using updated labeling and 100% of users successfully performed the task.

3. User's Symptoms Do Not Match the CGM Value (Critical): In this scenario, users were told that they had just woken up in the middle of the night because they felt shaky and sweaty, like when their blood sugar was low; they were also provided with a receiver/phone that showed a glucose value of 110 mg/dL with a horizontal trend arrow (reflecting stable glucose values changing at less than 1 mg/dL/min). This scenario was

designed to assess whether users could recognize a situation in which their CGM results might be incorrect and whether they would know how to make an appropriate treatment decision. Ninety-four percent (94%) of users stated that in this situation they would determine their treatment based on their symptoms and test their blood sugar with a meter rather than rely on the CGM system. However, three (3) participants indicated that they would ignore their symptoms and go back to sleep because the trend graph and trend arrow on the CGM appeared steady. Failure of this critical task suggests that some users understood that they should rely on CGM information rather than their own symptoms. Dexcom addressed failure of this critical task by modifying their training material to further emphasize that users should not ignore their symptoms. The modified training materials were reassessed in Dexcom's second summative study with 49 users. Ninety-eight percent (98%) of these users passed this scenario in this second study; 1 user did not recognize the CGM value as being inaccurate, which was recorded as a failure of the task. This user also indicated that they would eat crackers if they continued to feel symptomatic and Dexcom determined that this was acceptable.

4. Using CGM Values to Determine a Treatment Decision – Error Message Present (Critical): In this scenario, users were informed that they were sitting down to lunch and ready to bolus insulin. Their receiver/phone showed no current CGM data or data for approximately the past 90 minutes and it also displayed a "triple question marks" error. This scenario was designed to assess whether users could recognize a case in which they should not use CGM information for treatment. Ninety-eight percent (98%) of the users stated that in this case they would rely on their SMBG to determine a meal-time insulin dose rather than their CGM due to an error message and data gap. One participant stated that he was aware of the proper action (to not rely on the CGM and get an SMBG measurement instead); however, the user knowingly committed an error by choosing to not take an SMBG reading. This scenario was re-assessed in a second summative study using updated labeling and 100% of users successfully performed the task.

5. Update Calibration – User Obtains an Inaccurate SMBG Value (Critical): In this scenario, users were informed that after starting a snack of a sweet and sticky donut they remembered that they forgot to take insulin. Their CGM showed a value of 162 mg/dL and a horizontal trend arrow, and also a calibration icon. Users were informed that after taking a fingerstick test with SMBG (to calibrate their CGM) their SMBG showed a value of 291 mg/dL. This scenario was designed to assess whether users could recognize a situation in which their SMBG value might not be appropriate to use for CGM calibration (because the SMBG meter result was artificially high from sugar on their hands). Ninety-six percent (96%) of the users were able to correctly detect an inaccurate SMBG reading and said that they would wash their hands and recheck their SMBG value. Two (2) participants did not recognize the potential SMBG inaccuracy

and stated they would use the erroneous SMBG to calibrate their CGM. These participants also stated that they would use the SMBG blood glucose value to calculate an insulin dose, perhaps reflecting general confusion by these users with appropriate technique for obtaining an accurate SMBG value. [FDA notes that this scenario appears to assess the use of SMBG more than the use of CGM]

6. Using CGM Values to Determine a Treatment Decision – No Sequential Readings Present (Critical): In this scenario, users were informed that for the past few hours their CGM has been displaying occasional error messages, such as the "triple question marks" error. Users were also informed that they were about to eat a snack requiring an insulin dose and that their CGM showed gaps in recent CGM data, and a current CGM value of 280 mg/dL and no trend arrow. This scenario was designed to assess whether users understood the type of information that should be available on their CGM in order to make a treatment decision. Ninety-one percent (91%) of subjects correctly identified that they should not use information displayed on the CGM to make treatment decisions if sequential readings and trend arrows were not present. Two (2) users stated that they would make a decision based on their CGM and demonstrated no knowledge of the information that should be available (trend arrow, three sequential data points) in order to make a decision. Two (2) users stated that they were aware of the necessity of sequential readings and trend arrows but that they would make a decision based off CGM information anyway. Dexcom addressed failure of this critical task by modifying their training material to further emphasize that users should not ignore their symptoms. The modified training materials were reassessed with 49 users in a second human factors study; Ninety-two percent (92%) of users passed this scenario in this additional study; One (1) user did not recognize that without a trend arrow they should not use CGM for decision making; two (2) users stated that they currently use CGM non-adjunctively and that they would use a CGM value with no trend arrow for treatment decisions, one (1) user stated that they recognized that they should not use the CGM value in this situation but said they would use it anyway.

Prior to the study, Dexcom set their acceptance criteria for critical tasks at 100%. Some critical tasks in this study were not performed with 100% success, despite modifications to labeling and reassessment of those enhanced instructions. Following the study, Dexcom indicated that failures of these critical tasks were acceptable. For example, in one case (Scenario 3) where users ignored their hypoglycemia symptoms and said they would go back to sleep because of a stable CGM reading at a normal glucose value, Dexcom indicated that this is also possible with SMBG, where users might ignore their own hypoglycemia symptoms if they received an incorrect normal SMBG value. Dexcom also indicated that users might react differently in real life when actually experiencing hypoglycemic symptoms than in a hypothetical situation like the testing scenario. In other cases (Scenarios 4 and 6) users stated that they were aware of what they should do but that

is not how they would actually act. Since these users understood the correct actions but did not take them, Dexcom concluded that the training was effective for these individuals and scenarios. In another case (Scenario 5) where users failed to recognize they should not use an incorrect meter value for calibration, this resulted from users being unaware that their meter accuracy could be affected by washing their hands and therefore did not reflect a CGM labeling/training failure.

In their second summative study, Dexcom incorporated two additional scenarios that were not present in the first summative study in order to assess the risks of insulin stacking with both SMBG and non-adjunctive CGM. In each case, users were told that approximately one hour after eating a meal—for which they took an appropriate insulin dose—they checked the blood sugar with SMBG (in one scenario) or with CGM (in another). Users were then presented with a high SMBG value or a high CGM value (with a horizontal trend arrow). For the SMBG scenario, six (6) users stated they would give themselves a full correction dose of insulin and one (1) user stated that they understood the concept of insulin stacking but would administer a full correction dose anyway. For the CGM scenario, one hundred percent (100%) of users passed the scenario. Note that no training specific to SMBG use was provided as part of this study.

iii.   *Summary and Items for Panel Discussion*
The results of this human factors study highlight that interaction of users with CGM information may be a major point where non-adjunctive CGM introduces risk. The study also identified some specific challenges that users may face when basing their diabetes treatment decisions on CGM information. For example, users may not understand that issues related to SMBG accuracy may also impact CGM function (hand washing before testing), users may not understand when to use or not use CGM information, users may not understand when it is appropriate to calibrate their CGM with a blood glucose meter value, and in some cases users may understand that CGM information should not be used in a particular way, but choose to use the information anyway. In addition, Dexcom did not assess in this study whether users understand how to properly interpret trend information to determine the proper insulin dose (or whether their healthcare providers understand how to coach them in doing so).

The human-factors related risks of non-adjunctive CGM use may vary based on user group (self-managed adult, adolescent or child with diabetes, caregiver of a child with diabetes, caregiver of an older adult with diabetes, naïve vs. experienced CGM user, newly diagnosed diabetes vs. longer duration of diabetes,, technological savvy, numeracy skills, extent of training, etc.). Different users may also be exposed to different levels of training and training materials (untrained, formal or informal self-training, peer training, group training, one-on-one training with a professional; with written labeling, computer tutorials, hands on demonstration, etc.). The Agency requests that the panel discuss the human factors studies conducted by Dexcom and discuss whether the appropriate user groups and

training options have been evaluated to allow an assessment of whether users will know how to safely incorporate G5 CGM use in their diabetes management, and how to interpret glucose trend and rate of change information when making insulin dosing decisions.

In addition, there do not appear to be generally accepted clinical guidelines or recommendations in the clinical community for how glucose trend information should be taken into account when making treatment decisions with CGM. This issue was not specifically addressed by Dexcom in their human factors studies and therefore it is unclear whether users will know how to appropriately use non-adjunctive CGM information in determining treatment. The Agency requests that the panel discuss the need for developing, validating and providing recommendations for users (and the optimal format of this information) on how to incorporate glucose trend information into treatment decisions. For example, should explicit recommendations be developed and validated in human factors (or other) studies, should Dexcom provide available literature recommendations or references (if they are available), would more general "common sense" recommendations on using trend information be appropriate, or should determining how trend information is used be entirely at the discretion of users, or individually determined through patient-provider discussion? FDA would also like the panel's input on Dexcom's role in providing appropriate labeling/training on using trend information.

VII. Postmarket Data

Understanding the potential risks of non-adjunctive CGM use can be informed by an analysis of post-market signals, including adverse event surveillance and device recalls, related to Dexcom CGM devices.

i. *Medical Device Reports*

Analysis of Medical Device Reports (MDRs) submitted to FDA for adverse events associated with CGMs (product code MDS) and glucose test systems (product codes CGA, LFR and NBW) is presented below. MDRs are submitted by device manufacturers, user facilities (e.g., hospitals), healthcare providers, and consumers. The MDR volume for both CGMs and glucose meters are among the highest volume of MDRs submitted to the agency for any device. This may be due to the large population of people with diabetes in the US, the significant risks people with diabetes face every day, and the widespread use of these devices in diabetes management and care. The large volume of adverse event reports associated with these devices is also consistent with the criticality of the information they provide and the extent to which people with diabetes depend on these devices on a routine basis.

Notably, Dexcom is not the only CGM manufacturer but generates the majority of MDRs reported under the CGM product code. However, the other US CGM manufacturer,

Medtronic, has some CGM devices approved under the CGM product code, but MDRs for their newest sensor are reported under the product code for threshold suspend devices (product code OZO). Therefore, it is difficult to directly compare adverse event rates between CGM manufacturers based on this analysis. MDR report number is also related to the absolute number of device users, which may differ by manufacturer and device.

Note also that some additional Dexcom CGM related MDRs may be represented under other product codes because Tandem and Animas (manufacturers of insulin pumps that can display CGM values from the Dexcom sensor) report MDRs under insulin pump related codes, and so any Dexcom sensor related reports from these other devices (Animas Vibe and Tandem G4) may not be represented in this analysis, since there may be a delay in transmitting this information from Tandem and Animas to Dexcom for independent reporting by Dexcom under the CGM product code.

Figure 23: MDR Summary for CGM devices

Year	All CGM Manufacturers					Dexcom				
	MDRs (total)	Malfunctions	Serious Injuries	Deaths	Other/No Value	MDRs (total)	Malfunctions	Serious Injuries	Deaths	Other/No Value
*2016	38042	37127	839	69	7	35902	35033	800	67	2
2015	43901	42533	1270	77	1	43040	42159	805	76	0
2014	27327	26325	987	12	3	25831	25443	378	10	0
2013	13352	12799	540	1	12	13135	12744	380	1	10
2012	2050	761	1208	9	72	**773	492	206	4	71
2011	6471	2138	4099	83	151	**369	86	141	0	142

*Year to date (6 months)

**The large increase in MDRs from Dexcom starting in 2103 may be the result of two Warning Letters Dexcom received in 2010 and 2014, respectively. Both letters stated that Dexcom failed to report MDRs appropriately per 21 CFR Part 803.

For comparison, Figure 24 below summarizes the number of MDRs for glucose test systems. This analysis includes reports for laboratory instruments that measure blood glucose as well, but the reports are predominantly reports related to blood glucose meters.

Figure 24: MDR Summary for glucose test systems

	Glucose Test Systems				
Year	MDRs (total)	Malfunctions	Serious Injuries	Deaths	Other/No Value
*2016	35780	34473	1193	5	109
2015	65240	62627	2360	8	245
2014	42480	39937	2316	10	217
2013	38424	35696	2503	12	213
2012	27750	24792	2863	5	90
2011	27993	24510	3345	15	123

*Year to date (6 months)

ii. *Recalls*

Dexcom recently announced a Class I recall of their G4 and G5 CGM devices because of intermittent or complete failure of the audible alarm feature in some devices. For users who rely on the audible alarm (rather than vibration alarm), this reduces the available benefit of the CGM because users are less likely to be notified of hyperglycemia or hypoglycemia by high or low glucose threshold alerts.

VIII. Summary

FDA has recently approved changes to the Dexcom G5 Continuous Glucose Monitoring System device that have resulted in increased clinical accuracy compared to accepted reference glucose testing methods. The current level of accuracy is close to, but not as good as, typical self-monitoring blood glucose meters in the U.S. market. However, the Dexcom G5 Continuous Glucose Monitoring System provides contextual information that self-monitoring blood glucose meters do not provide that may lead to users making more informed insulin dosing decisions, and which in turn may allow for better glucose management and outcomes. Significant numbers of Continuous Glucose Monitoring System users are believed to be currently using glucose values obtained from their Continuous Glucose Monitoring System devices ("off label" use) to make insulin dosing decisions. A significant barrier to these users making better, informed decisions using glucose data from their Dexcom G5 Continuous Glucose Monitoring System device is the labeling restriction currently in place that this device is only to be used adjunctively. FDA offers the following discussion questions to the panel for consideration of whether it would

be appropriate to allow for labeling for non-adjunctive use for the Dexcom G5 Continuous Glucose Monitoring System:

IX.   Questions for the Panel

Discussion questions

1. Modeling

    Please discuss whether the clinical accuracy studies, and modeling based on these clinical accuracy studies, is adequate to provide reasonable assurance of safety and effectiveness for the proposed indications for use for the Dexcom G5 Mobile Continuous Glucose Monitoring System. If not sufficient, please discuss the following sub-topics:

    a) If the modeling is insufficient, as conducted, but would if conducted adequately provide reasonable assurance of safety and effectiveness for the proposed indications for use for the Dexcom G5 Mobile Continuous Glucose Monitoring System, what deficiencies in the conducted modeling are evident (e.g. modeling methodology, modeled use and/or physiological scenarios, modeled populations)?
    b) If modeling would be insufficient, alone, even if conducted adequately, what type(s) of study(ies) would be sufficient to provide reasonable assurance of safety and effectiveness for the proposed indications for use for the Dexcom G5 Mobile Continuous Glucose Monitoring System?

2. Human Factors

    Please discuss whether users will know how to safely incorporate Dexcom G5 Mobile Continuous Glucose Monitoring System glucose trend and rate of change information when making insulin dosing decisions. If you do not believe that users will know how to safely incorporate Dexcom G5 Mobile Continuous Glucose Monitoring System glucose trend and rate of change information when making insulin dosing decisions, please discuss the following sub-topics:

    a) What information would users require to safely incorporate Dexcom G5 Mobile Continuous Glucose Monitoring System glucose trend and rate of change information when making insulin dosing decisions?
    b) Would a training requirement for the Dexcom G5 Mobile Continuous Glucose Monitoring System allow users to safely incorporate Dexcom G5 Mobile Continuous Glucose Monitoring System glucose trend and rate of change information when making insulin dosing decisions, and if so, what type of training is recommended?
    c) If, for the general population, the risk to safe and effective non-adjunctive use may be mitigated by information provided in 2 a) and/or training provided in 2 b), above, are there any user sub-populations for which these mitigations would not sufficiently reduce risk to safe and effective non-adjunctive use (e.g. pediatric users, newly-diagnosed users)?

Ballot Questions

3. Is there reasonable assurance that the Dexcom G5 Continuous Glucose Monitoring System is safe for the proposed indications for use?
4. Is there reasonable assurance that the Dexcom G5 Continuous Glucose Monitoring System is effective for the proposed indications for use?
5. Do the benefits of the Dexcom G5 Continuous Glucose Monitoring System for the proposed indications for use outweigh the risks of the Dexcom G5 Continuous Glucose Monitoring System for the proposed indications for use?

X.   Appendices:

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