



**July 21, 2016 meeting of the
Clinical Chemistry and Clinical Toxicology Devices Panel**

P120005/S041

**Dexcom G5 Mobile Continuous Glucose Monitoring System
Dexcom, Inc.**

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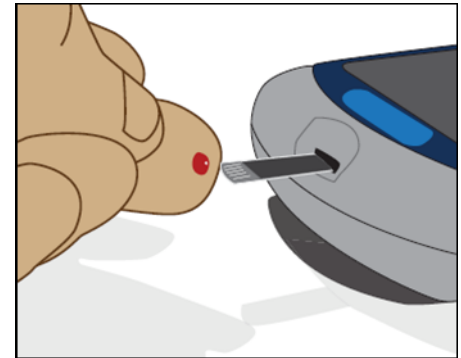
Division of Chemistry and Toxicology Devices
Office of *in vitro* Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration



Diabetes: standard of care

Currently, patients with diabetes make treatment decisions to manage their body's glucose by periodic testing with self-monitoring blood glucose meters (SMBG)

- Patients do this via “finger sticks”
- The number of “finger-sticks” performed varies patient-to-patient.



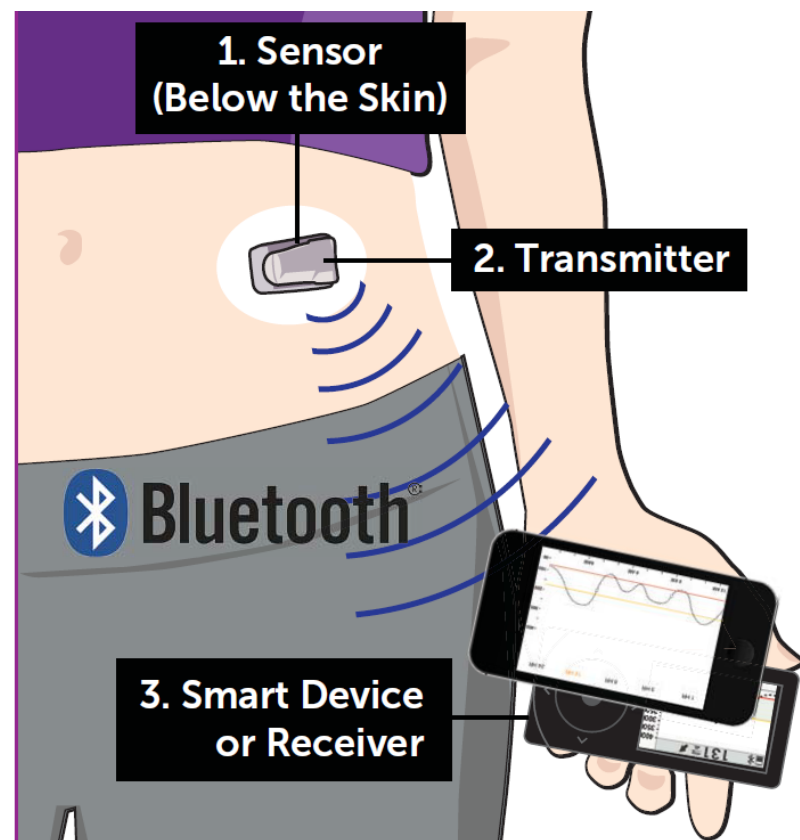
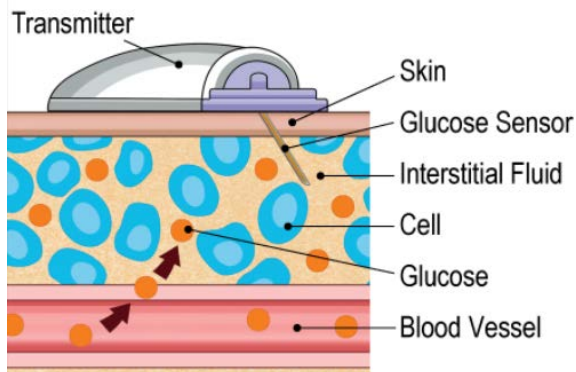
Typical SMBG accuracy

- Currently marketed SMBG devices are relatively accurate compared to established laboratory methods.
- Various studies have shown that SMBG devices typically have MARDs from 5-9%.
 - MARD = mean absolute relative difference; a broad measure of accuracy
- Accuracy at low end of glycemic range is important for making treatment decisions regarding potential hypoglycemia
- Accuracy at high end of range important for making treatment decisions regarding potential hyperglycemia

Dexcom G5 CGM

G5 Continuous Glucose Monitoring (CGM) system:

- glucose sensor
- transmitter
- receiver device

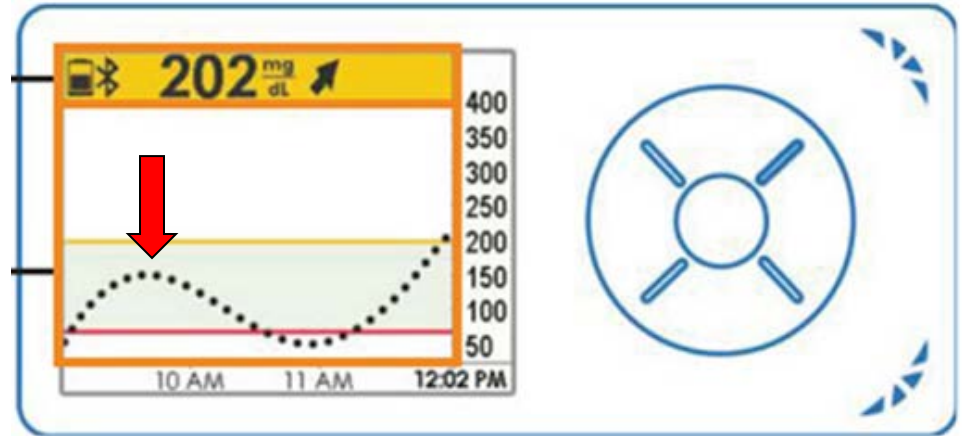


Current G5 Indications

➤ *FDA Approved Device*

Current Intended Use

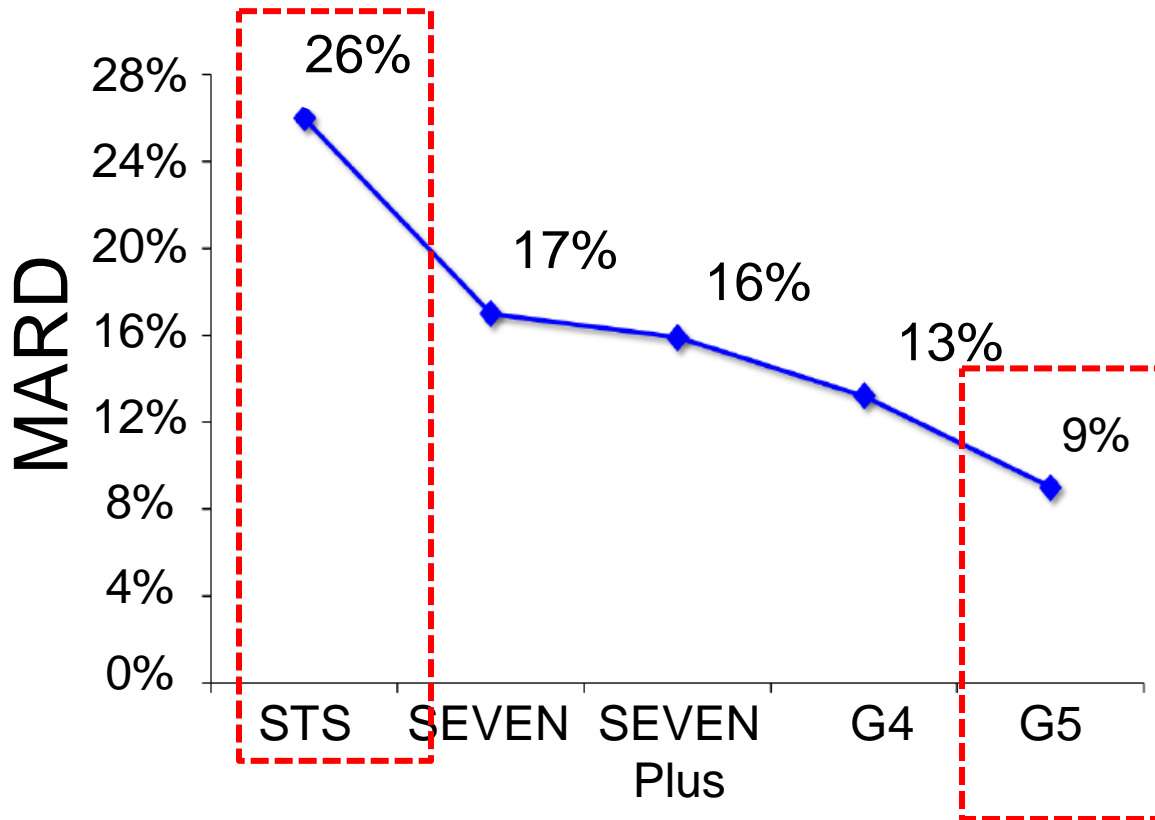
- ≥ 2 years of age
- Tracking and trending (**adjunctive use**): Use the historic glucose trend information to complement SMBG for making diabetes management decisions



For example: user might look back at recent treatment to evaluate how their body reacted to that treatment.

Dexcom CGM accuracy

CGM system accuracy has continuously improved (for reference, the Dexcom STS CGM was approved in 2006)



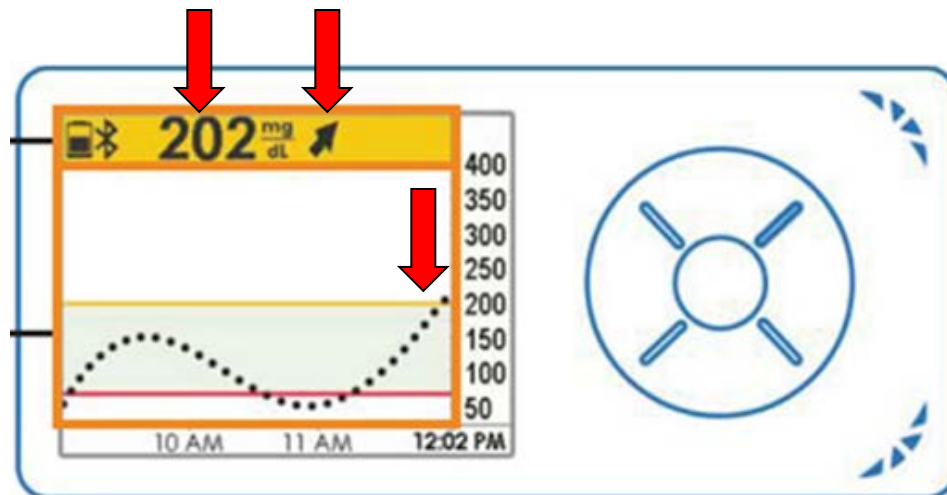
SMBG accuracy*
MARD of
approximately 5-9%

*Tack *et al*, 2012; Zueger *et al*, 2012;
Kuo *et al*, 2011.

Proposed change to G5 indications

Proposed Intended Use:

- ≥ 2 years of age
- **Non-adjunctive**: Use the current glucose information (values and trends) to make real-time diabetes management decisions



i.e., a user might make a real-time treatment decision based on the current glucose value along with information from the trend graph and trend arrow.

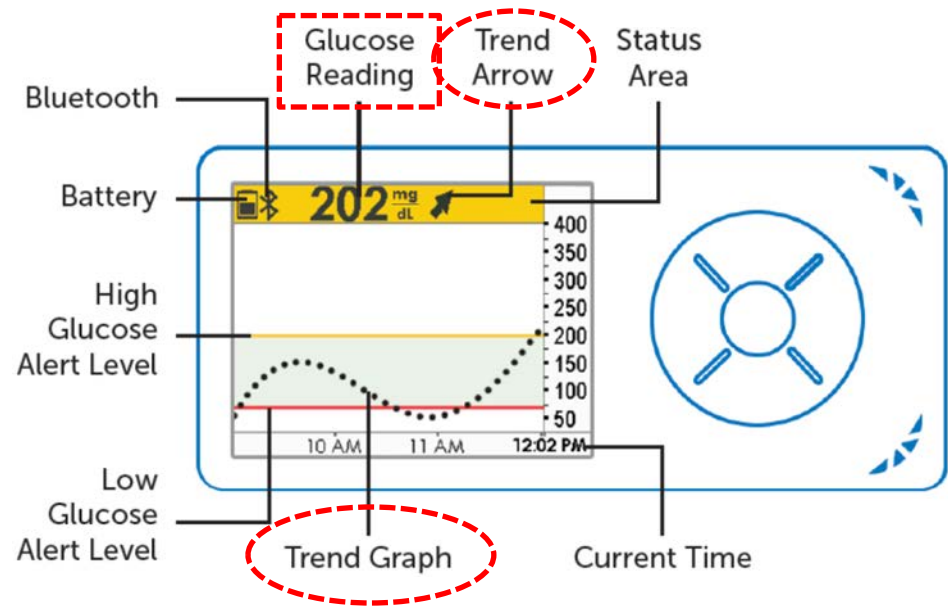


Purpose of Panel Meeting

FDA would like feedback from the panel regarding whether the benefits of the Dexcom G5 CGM System outweigh the risks for the proposed intended use.

G5 non-adjunctive benefits

In addition to point glucose readings, Dexcom's G5 CGM also provides information on glucose trend via a trend arrow and graph.










G5 non-adjunctive risks

System-based

- Relative inaccuracy compared to SMBG

Human Factors-based

- Potential for incorrect treatment decisions based on glucose trend information

Trend Arrow on CGM Display	
Double arrow up	
Single arrow up	
45° arrow up	
Flat arrow	
45° arrow down	
Single arrow down	
Double arrow down	

Studies Dexcom conducted

- **Sensor Accuracy Studies (Pediatric and Adult)**
 - Previously conducted to demonstrate G5 CGM sensor accuracy
- **Computer Simulations**
 - To simulate potential risks of Dexcom G5 CGM-based treatment decisions (“non-adjunctive” use)
- **Human Factors Studies**
 - To understand usability-based risks

Clinical trial limitations

- A clinical study to demonstrate safety and effectiveness for this new indication would have meant a large, prospective observational trial.
 - Value of a large scale trial evaluating safety and effectiveness of G5 non-adjunctive use unclear
 - Consider alternative approaches

Dexcom G5 system accuracy

Dexcom conducted 2 clinical trials:

- 50 Adult subjects (18-85 yr.)
- 79 Pediatric subjects (2-17 yr.)

Study participant glucose levels were manipulated to challenge the device range

- Exercise challenges (raise glucose)
- Glycemic challenges (carbohydrates, insulin)

G5 concurrence to true glucose

<u>mg/dL</u>	<u>Adult</u>	<u>Pediatric</u>
40-60	89%*	54%
61-80	91%	77%
81-180	92%	88%
181-300	93%	96%
301-350	94%	91%
351-400	92%	81%

Studies of SMBG accuracy typically show 95% or better concurrence across this range

*CGM readings that were within 20% of the true glucose value (or within 15 mg/dL for readings less than 80 mg/dL).

G5 readings with high bias

<u>mg/dL</u>	<u>Adult</u>	<u>Pediatric</u>
40-60	0%*	3%
61-80	0%	3%
81-180	1%	1%
181-300	1%	1%
301-350	1%	5%
351-400	0%	8%

*CGM readings that were greater than 40% from the true glucose value (or 40 mg/dL for readings less than 80 mg/dL).

Computer simulations

Dexcom conducted two different computer simulations:

Meal-time dosing simulation:

- Dexcom developed (Monte Carlo method)
- Focused on meal-time insulin dosing decisions
- Evaluated hyperglycemia (>180 mg/dL) and hypoglycemia (<70 mg/dL)

2 week simulation:

- UVA/Padova simulator
- Meal time dosing, correction boluses, hypoglycemia treatment
- Evaluated various glycemic control metrics

Advantages/limitations

“All models are wrong, but some are useful”

-George Box, Statistician

Advantages:

Can simulate the impact of multiple variables (system, behavioral, physiological) in isolation and simultaneously, in ways that would not be possible in a clinical trial.








Limitations:

Simulations have constraints/assumptions (e.g. insulin dosing decisions) that may not reflect all real-world use/conditions/physiology/biology

Meal-dosing simulation

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

Insulin dosing assumptions:

Simulated CGM "Measured" Pre-prandial ROC	Trend Arrow on CGM Display	Insulin Adjustment Factor (IAF)
$ROC \geq 3$	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
$-2 < ROC \leq -1$	45° arrow down 	0.9
$-3 < ROC \leq -2$	Single arrow down 	0.8
$ROC \leq -3$	Double arrow down 	0.7

- Insulin dose adjustment using trend arrows was standardized
- SMBG users had no knowledge of glucose rate-of-change or post-meal glucose levels (**i.e. IAF =1**); this impacted their dosing decisions and hypoglycemia risk mitigation.

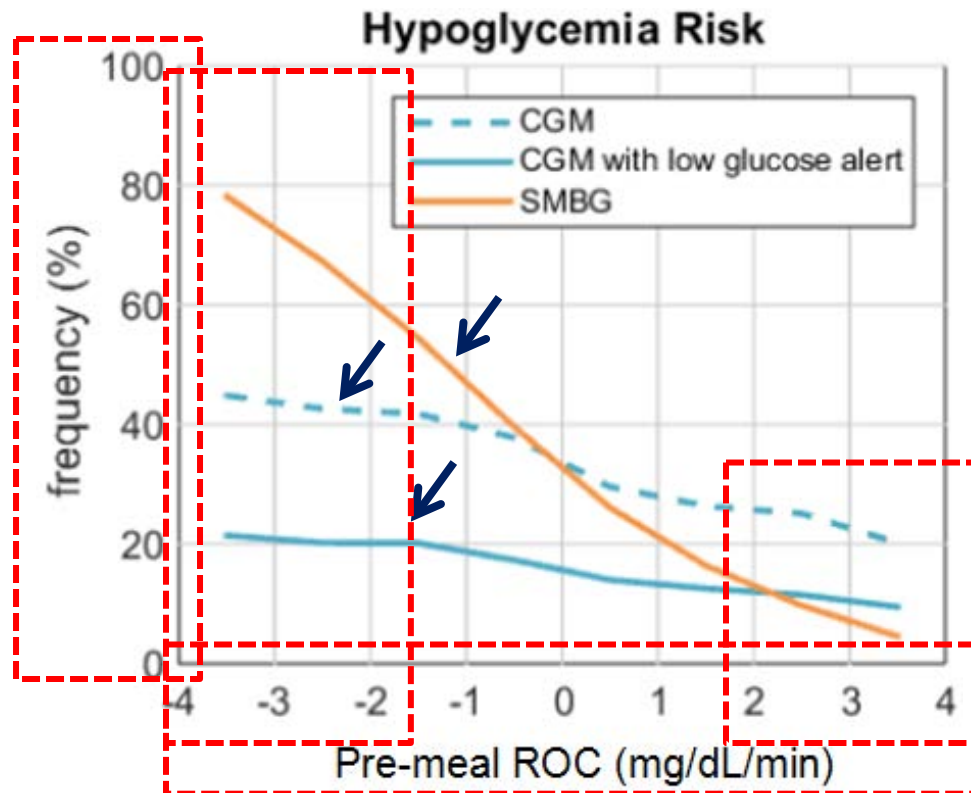
Simulated meal-time dosing risk

Two steps for evaluation of simulated hypoglycemia risk:

1. Post-meal glucose levels were calculated
 - Incorporated errors from SMBG or CGM inaccuracy
 - If post-meal glucose was <70 mg/dL, then this was considered hypoglycemia risk (post-meal target glucose was set at 100 mg/dL)
2. Risk mitigation by CGM hypoglycemia alerts was calculated
 - Alerts were modeled based on CGM accuracy, with a setting of 70 mg/dL
 - All timely alerts were assumed to mitigate hypoglycemia risk 100% of the time

Meal-dosing results, nominal

Simulations were performed for 50,000 virtual subjects



Examples of other risk cases

Insulin dosing

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

More aggressive adjustment



- **Modeled a more aggressive trend adjustment**
- Higher hypoglycemia risk relative to SMBG

Insulin dosing

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

Rate of change error



- **Modeled additional error in the rate of change**
- Higher hypoglycemia risk relative to SMBG when errors resulted in a larger insulin dose

Meal-dosing simulation value and limitations

- Tens of thousands of virtual subjects evaluated
- 20 different modeling parameters were assessed
- Relatively simple simulation
- Assessed risks of insulin dosing for a single meal
- Limited user behaviors simulated
- Standardized use of trend information for dosing
- Only hypoglycemia alerts mitigated hypoglycemia
- Did not explicitly identify conditions under which risks of G5 use would be unsafe

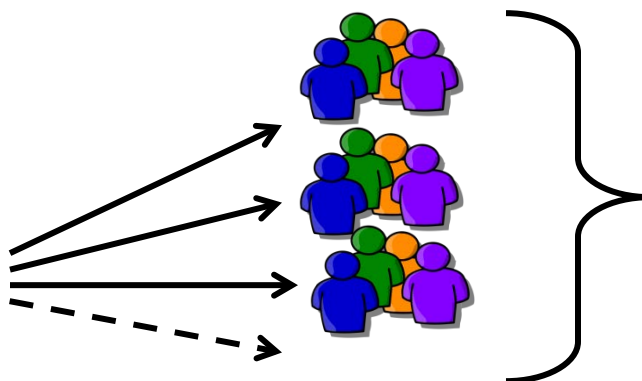
Meal-dosing simulation summary

- Dexcom modeled hypo and hyperglycemia risk related to meal dosing
- In general: elevated hypoglycemia risk (relative to SMBG) for non-adjunctive use at high positive rates-of-change
- The simulation results reported that alerts/alarms largely mitigated hypoglycemia risk
- FDA requests the panel consider the overall value of these simulations in informing an understanding risks of real-world non-adjunctive G5 CGM use

2-week simulations overview



Virtual subjects
Physiologically defined
(100 adult, 100 pediatric)



Assign behaviors
Repeat 100 times for
adult and pediatric

Two cohorts:
10,000 adult and
10,000 pediatric
virtual subject
behaviors (VSBs)



Hypoglycemic
aware and
unaware
populations

2-week simulation scenarios



Physiologically and behaviorally defined virtual subjects

- Meal dosing
- Correction boluses
- Hypoglycemia treatment



Two weeks of diabetes management

Treatments based on:

- SMBG
- CGM

Analysis

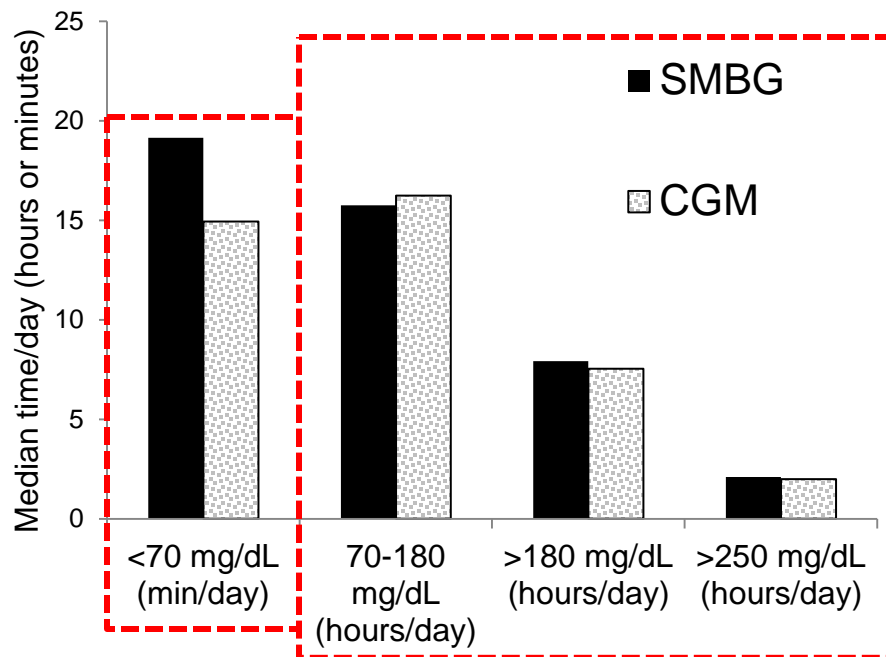
- Time and # of events below 50 and 70 mg/dL
- Time between 70-180 mg/dL
- Time above 180 and 250 mg/dL

2-week simulation assumptions

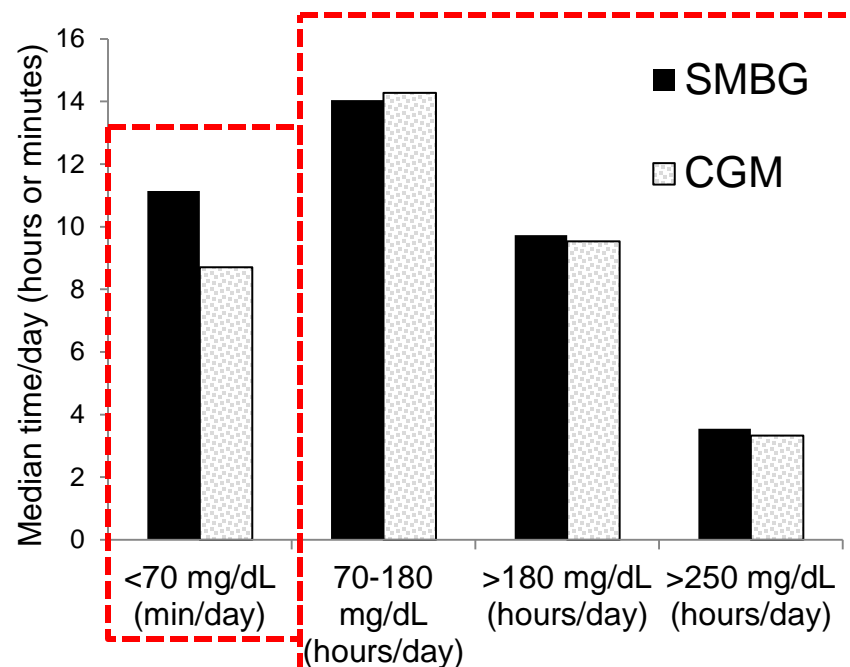
- No learning
- No exercise
- No CGM naïve vs. experienced
- Target glucose value set at 120 mg/dL
- Regular CGM calibration
- Frequency of CGM checks
 - Pre- and 120 minutes post-meal
 - Pre-sleep and following CGM alerts
- Frequency of SMBG checks
 - Minimum 4 per day
- Standardized use of trend CGM information
 - Adjust BG by ± 25 mg/dL or ± 50 mg/dL depending on rate of change

2-week simulations results

Adult



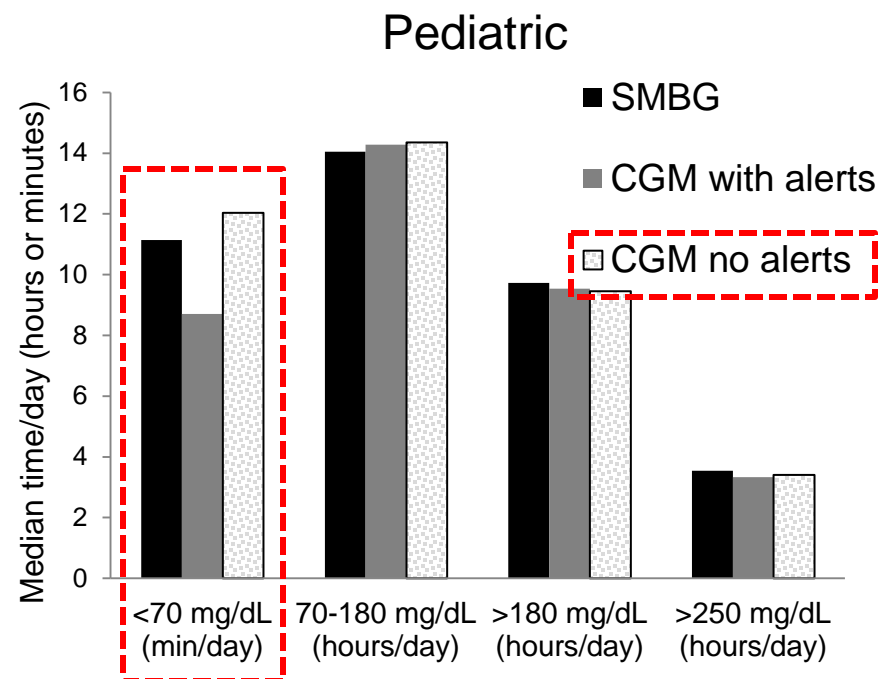
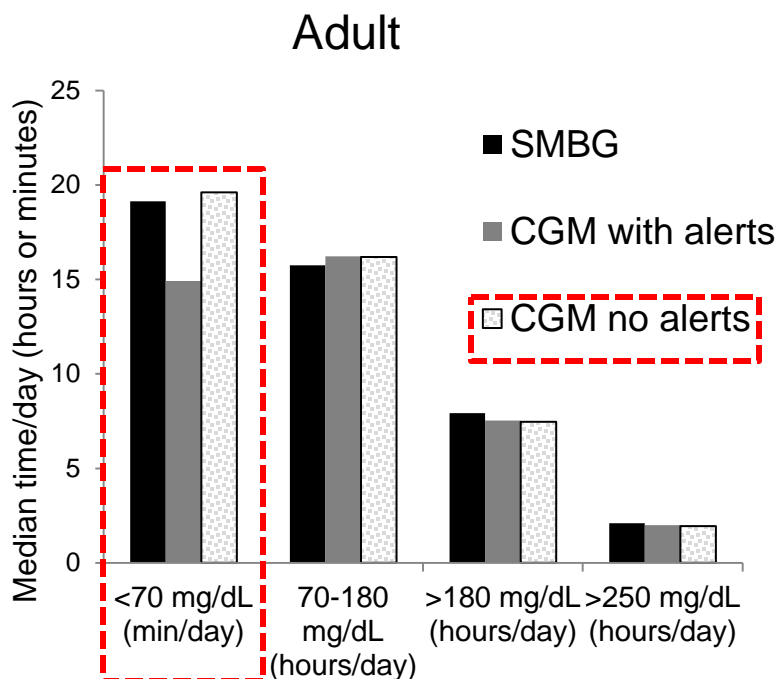
Pediatric



- *Rate of events* <70mg/dL increased although duration was decreased
- Results on day 1 (known worse sensor performance) comparable

Results: with alerts vs. no alerts

Alert settings:
 ≈1/4 of virtual subjects set 70 mg/dL
 ≈2/3 of virtual subjects set 80 mg/dL
 ≈15% had no alert (used the fixed 55mg/dL alarm)



2-week simulations summary

- Large and diverse virtual patient population
- Pre-meal and correction boluses, hypoglycemia
- General improvement in median time spent at specific glucose levels/ranges
- Benefit of less median time $<70\text{mg/dL}$ was dependent on optional low glucose alerts
- Assumptions about user behaviors
- FDA request the panel consider the overall value of these simulations in informing an understanding of risks of real-world non-adjunctive use



Simulations: discussion questions for the panel

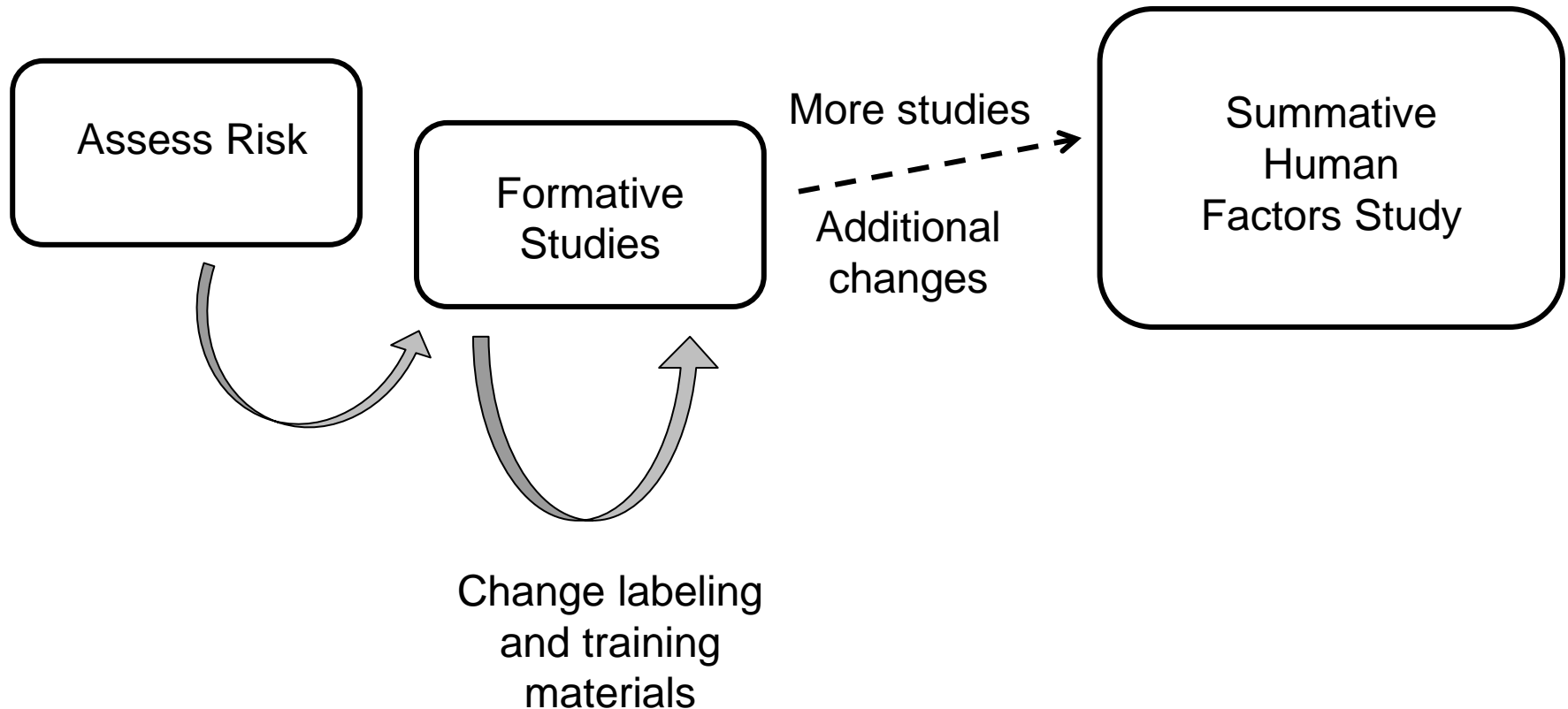
Please discuss whether the clinical accuracy studies, and modeling based on these clinical accuracy studies, is adequate to provide reasonable assurance of safety and effectiveness for the proposed indications for use for the Dexcom G5 Mobile Continuous Glucose Monitoring System. If not sufficient, please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

Human Factors non-adjunctive G5 risk

- Human factors: *interaction with medical device technology*
- Non-adjunctive G5 CGM – risks related to extraction and use of information
- Human factors assessment includes:
 - How will CGM information be used when making treatment decisions – what are the risks?
 - Design to mitigate risk (e.g., labeling and training design)
 - Test
- Human factors testing: a useful tool for highlighting and mitigating user behavior associated risks


G5 CGM Human Factors studies




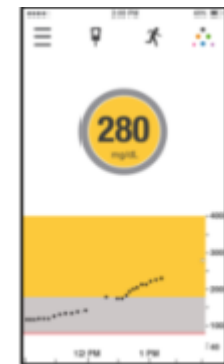
Human Factors study design

- Risks assessed:
 - Users not responding to alerts
 - Using CGM information to make a treatment decision when incomplete information available
 - Inappropriately trusting CGM information over symptoms when making treatment decisions
- Test Participants (diabetes managed with insulin)
 - Self-managing adults
 - Self-managing children and adolescents
 - Caregivers managing therapy for children with diabetes
- Training
 - One-on-one with a Dexcom trainer and the G5 Getting Started Guide
 - Self-trained with a computer-based interactive tutorial
 - No training

Human Factors study examples

- Risk: Users ignore symptoms
 - Wake up at night with symptoms of low blood sugar, CGM shows 
 - Some participants stated they would ignore their symptoms and go back to sleep

- Risk: Use CGM when not enough information available
 - CGM results have been intermittent, check CGM prior to eating a snack, CGM shows 
 - Some participants would use the value despite no trend arrow



Human Factors summary

- Identified and assessed some risks associated with non-adjunctive CGM
- Tested various user groups and training levels
 - Training reduced some risks
- No explicit assessment of some user groups and training
 - Other user groups
 - Technological savvy, low numeracy skills, etc.
 - Other training paradigms
 - Informal self or peer training
- Risks not assessed
 - How would trend information actually be used?
 - Impact of readily available glucose values



Human Factors: discussion questions for the panel

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 “a” and/or training provided in “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 for the panel

- Is there reasonable assurance that the Dexcom G5 Continuous Glucose Monitoring System is safe for the proposed indications for use?
- Is there reasonable assurance that the Dexcom G5 Continuous Glucose Monitoring System is effective for the proposed indications for use?
- 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?



Thank you!