CLOSER LOOK

MEMORANDUM

## FDA releases special controls for 510(k) "integrated CGM" as part of Dexcom G6 clearance: high bar for accuracy - April 3, 2018

**Executive Highlights**

- **As part of clearance for Dexcom's no-cal G6 last week, the FDA has created a lower-risk 510(k) pathway for integrated CGM ("iCGM") - including "special controls" to ensure safety/effectiveness and interoperability.** The big focus of the special controls are performance standards, with iCGMs expected to reliably measure within the 15/15 margin at all glucose ranges: >70% of CGM values within ±15% of reference for 70-180 mg/dl; >85% within ±15 mg/dl for <70 mg/dl; and >80% within ±15% for >180 mg/dl. FDA expects iCGMs to exceed these benchmarks for the lower bound of the one-sided 95% confidence interval - this very smart framing is to ensure that clinical studies are large enough to demonstrate small sensor variability and bias. There are also accuracy standards for ± 20%/20 mg/dl (>87% of points) and ±40%/40 mg/dl (>98% or >99%), as well as a rate-of-change, mandatory shutoff, manufacturing lot release criteria, and data transmission requirements.
- **Based on our read of their labeled accuracy, Abbott and Medtronic do not appear to qualify as iCGMs at this time. Senseonics appears to meet the bar, depending on what studies are included.** FreeStyle Libre (real-time) falls short of the hypoglycemia standard, while Medtronic's Guardian Sensor 3 (two cals/day) slightly misses the outlier requirements for euglycemia and hyperglycemia. Senseonics' Eversense looks to meet the hypoglycemia benchmark (and all others) if data from the PRECISE II and PRECISION studies are pooled. Since current CGMs' labels don't align with the thresholds for iCGMs, there is some subjectivity to this analysis, and it's impossible to be certain. We share what we have inferred below.
- **Beyond accuracy, mandatory shutoff and real-time glucose transmission are required,** meaning Guardian Sensor 3 (no mandatory shutoff) and FreeStyle Libre (does not communicate continuously) do not appear to qualify in their current forms for the iCGM pathway. Of course, the PMA pathway will still exist for CGM, and both companies may have other devices in the works that do hit the standards.
- **As noted last week, this is clearly a competitive advantage for Dexcom, as it creates a minimum accuracy moat for competitors - if you can cross the moat (like G6), you are rewarded with a lower-risk category to propel faster innovation with less regulatory burden.** The interoperability focus of iCGM - it is part of G6's indications for use! - could also allow for wider, easier integration of CGM with pumps, apps, and wearables. There is still uncertainty here, but it's a clear step towards FDA's vision of a plug-and-play, interoperable diabetes device ecosystem.
- **Below, we include enthusiastic interviews with Drs. Daniel DeSalvo, Henry Anhalt, Roy Beck, Zan Fleming, and Bruce Buckingham.** They all agreed that this new pathway is a "major game-changer" for the field, that it raises the bar on CGM accuracy, and that the interoperability implications are "amazing."

In tandem with last week's earlier-than-expected clearance of Dexcom's factory-calibrated G6 CGM, the FDA announced a new regulation for "integrated continuous glucose monitoring system," or "iCGM" for short. In this new pathway, iCGM systems will be down-regulated from a high-risk Class III (PMA) to a lower-risk class II devices (510(k) clearance) - a big change that will enable faster iterative innovation with less regulatory

burden for those that qualify. By definition, iCGMs are also FDA-cleared with interoperability in mind, a major step in the vision for plug-and-play devices that minimize regulatory burden.

This report explores the "special controls" to be classified as an iCGM, including minimum performance and interoperability requirements. FDA's goal with these special controls is to ensure iCGMs are safe and effective, even in the lower-risk 510(k) pathway. These standards are shared below and included in Dexcom's G6 FDA letter here.

Based on our interpretation, it does not appear that other companies' CGM systems currently meet the accuracy and/or interoperability standards. The information in current product labels does not give ALL the definitive information, but here's what we have inferred:

- **Abbott's FreeStyle Libre (real-time) does not appear to meet the hypoglycemia (<70 mg/dl) performance standard**, which requires accuracy within ±15 mg/dl over 85% of the time (lower bound of 95% confidence interval). In hypoglycemia, FreeStyle Libre is currently within ±15 mg/dl between 45%-72% of the time. Regarding interoperability, the current "flash" version of Libre also cannot transmit real-time data continuously to a separate device, so iCGM status will likely need to wait until the next-gen version.
- **Medtronic's Guardian Sensor 3 (GS3) appears to fall just short in euglycemia and hyperglycemia accuracy** (based on two calibrations/day, abdomen wear). GS3 is at 98.6% in euglycemia, just shy of the bar for >99% within ±40% in 70-180 mg/dl. In hyperglycemia (180 mg/dl), GS3 measures within the ±15% margin 76.9%-79.5% of the time, just shy of the >80% standard. GS3 also does not have a mandatory shutoff at this stage (i.e., it *can* be restarted), which is required for an iCGM.
- **Senseonics' Eversense appears to meet the accuracy requirements, including in hypoglycemia, if the PRECISE II and PRECISION studies are pooled:** ~83%-92% of points are within ±15 mg/dl in hypoglycemia ranges, which should exceed the >85% bar on a pooled basis. Based on PRECISE II alone, Senseonics falls a bit short on hypoglycemia. This is based on data presented last week at FDA with the improved algorithm.
- **Dexcom's G5 appears to meet all the iCGM performance requirements, though we'd be surprised if Dexcom goes back** and gets G5 cleared as an iCGM. Presumably Dexcom will focus on G6 going ahead, as that is the sensor of the future and G5 will presumably be phased out over time. Plus, G5 does not have a mandatory shutoff, which is an iCGM requirement.

Reading through the special controls (partially summarized below in the first table below) highlights the FDA's focus in CGM performance: a high % of values within 15% / 15 mg/dl of reference at all measuring ranges; minimizing big outliers (>40%); very strong accuracy in hypoglycemia; large enough clinical studies that result in fairly small confidence intervals (i.e., robust accuracy characterization with minimal sensor-to-sensor variability); and acquiring equally robust data in pediatrics. MARD does not appear anywhere, as the Agency's focus is clearly on % within ±15% / 15 mg/dl and within ±20% / 20 mg/dl.

Notably, FDA is focused on the lower-bound of the confidence internal that surrounds these accuracy percentages. Setting the performance standard in this way assures a suitably sized study - otherwise, a company could submit one patient for one hour and meet the bar. If a sensor is really precise, a smaller clinical study would be needed, but if the sensor has more variability, a larger study will be needed to demonstrate that the variability and bias are both acceptable.

As noted last week, the existing PMA process will remain in place for CGM. That said, we'd assume sensors that can meet the iCGM standards will move this way - the 510(k) path is more attractive from a speed and innovation perspective, especially as the field moves to interoperability. Future iCGMs will be able to send 510(k)s to the FDA and claim the G6 as a predicate device. AID systems will remain Class III devices, but G6 (and other iCGMs) can be a class II component of these systems. We're still unclear on how streamlined the path will be for a partner that talks to an iCGM, though we assume it will save some time and hassle.

The FDA deserves a lot of credit for paving this new regulatory path for CGM with Dexcom, which could be gamechanging for the field - allowing highly accurate, interoperable sensors to move faster in the 510(k) regulatory path could open a lot more innovation and will presumably prompt a faster move toward an interoperable device ecosystem.

Near-term, this is a clear competitive advantage for Dexcom's G6 as the only iCGM: the lower-risk classification will allow it to innovate faster with shorter/no submissions, and the specific special controls set a high bar for competitors to achieve. Plus, iCGM clearance for interoperability could certainly have implications for pump, smart pen, and automated insulin delivery innovation, as well as patient choice. We hope to see a day where a variety of iCGMs, iPumps, and iAlgorithms are on the market, with simpler submissions for components and a welcoming sandbox for innovation.

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## Special Controls - Accuracy and Performance

| **For iCGM Measurements in the Range of** | **Difference from Reference Blood Glucose** | **Performance Standard** (Benchmark) |
|---|---|---|
| 70-180 mg/dl | Within ±15% | **>70%** for lower bound of one-sided 95% confidence interval |
| 70-180 mg/dl | Within ±40% | **>99%** for lower bound of one-sided 95% confidence interval |
| Full device measuring range (e.g., 40-400 mg/dl) | Within ±20% | **>87%** for lower bound of one-sided 95% confidence interval |

| | | |
|---|---|---|
| <70 mg/dl | Within ±15 mg/dl | **>85%** for lower bound of one-sided 95% confidence interval |
| <70 mg/dl | Within ±40 mg/dl | **>98%** for lower bound of one-sided 95% confidence interval |
| >180 mg/dl | Within ±15% | **>80%** for lower bound of one-sided 95% confidence interval |
| >180 mg/dl | Within ±40% | **>99%** for lower bound one-sided 95% confidence interval |
| <70 mg/dl | No corresponding blood glucose value >180 mg/dl (i.e., 0%) | |
| >180 mg/dl | No corresponding blood glucose value <70 mg/dl (i.e., 0%). | |

- **iCGMs must also share the manufacturing lot release criteria - this is to ensure that sensors being made continue to meet the accuracy standards.** Similar to the issues raised for glucose test strips, this will prevent manufacturers from widening release criteria after clearance and putting out sensors that don't perform as labeled.

## Do Abbott, Medtronic, and Senseonics Meet the Performance Standards?

**The table below summarizes the labeled performance data for Abbott's FreeStyle Libre (US, real-time), Medtronic's Guardian Sensor 3, and Dexcom's G5 (we haven't seen the G6 pivotal data yet).** We've also included data presented at the FDA advisory committee for Senseonics' Eversense last week.

- **Two things are critical to note about this analysis: (i) confidence intervals are not currently reported in product labels; and (ii) the specific glucose bins above are not reported in labels right now. This makes it impossible** to know with certainty if these systems truly do meet the iCGM performance standards - hence used of the words "likely" below. The YES and NO designations below are based on our best guesses in looking at the labels, which are pasted after the following table. To be clear: the actual number reported in the label is shown below, though we recognize this is not the lower-bound of the 95% confidence interval (the actual FDA benchmark). In all cases, the glucose bins also don't align - for instance, accuracy in the special controls is measured at a threshold of <70 mg/dl, but the current product labels report accuracy in "40-50" and "51-80" mg/dl bins. We've put a range in relevant cases to indicate the overlapping bins. For euglycemia, we've simply used the range 81-180 mg/dl (currently in labels), though we recognize this is not 70-180 mg/dl. We've also included Dexcom's G5, just to give a sense of where it stands on accuracy relative to the other systems. Of course, there are also separate interoperability and other special controls to meet, as outlined in the subsequent sections below. The Senseonics column below includes accuracy from both US clinical studies - PRECISE II and PRECISION - presented as a low-to-high range of values.

| **Performance Standard: Lower bound of one-sided 95% confidence interval** | **Abbott FreeStyle Libre** | **Medtronic Guardian Sensor 3** 2 cals/day | **Senseonics Eversense*** Improved | **Dexcom G5** Software 505 Algorithm |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| | | | algorithm, 90-Day | |
| **Euglycemia:** >70% within ±15% for 70-180 mg/dl | YES 82.9% | YES 78.6% | YES 80.5%-85.6% | YES 84% |
| **Euglycemia:** >99% within ±40% for 70-180 mg/dl | YES 99.3% | Likely NO 98.6% | YES 99.0%-99.6% | YES 99% |
| **Overall:** >87% within ±20% over full device measuring range | YES 91.0% | Likely YES 88.2% | YES 92.8%-94.3% | YES 93% |
| **Hypoglycemia:** >85% within ±15 mg/dl for <70 mg/dl | Likely NO 44.7%-72.2% | Possibly YES 77.9%-87.3% | Likely YES* 83.3%-91.9% | YES 89%-91% |
| **Hypoglycemia:**>98% within ±40 mg/dl for <70 mg/dl | Likely NO 94.7%-97.6% | YES 99.7%-100% | YES 99.1%-99.6% | YES 100% |
| **Hyperglycemia:**>80% within ±15% for >180 mg/dl | Likely YES 77.0%-84.9% | Likely NO 76.9%-79.5% | YES 84.8%-96.8% | YES 80%-86% |
| **Hyperglycemia:** >99% within ±40% for >180 mg/dl | YES 99.7%-100% | Likely YES 98.9%-100% | YES 99.2%-100% | YES 99%-100% |

*Senseonics Eversense includes accuracy data from both US clinical studies, PRECISE II and PRECISION, shared in the FDA briefing documents last week (here and here). Based on PRECISE II alone, Senseonics meets all benchmarks except the >85% within ±15 mg/dl for <70 mg/dl hypoglycemia, where it falls just a bit short. However, PRECISION included more points in hypoglycemia, and we assume the ultimate label will include both data sets.

- **Abbott FreeStyle Libre (real-time) US label** - key accuracy data is in table 1 on page 108:

**Table 1: Number and Percent of Results within YSI Reference**

| CGM Glucose Level (mg/dL) | Number of CGM-Reference Pairs | Within ±15% / ±15mg/dL | Within ±20% / ±20mg/dL | Within ±30% / ±30mg/dL | Within ±40% / ±40mg/dL | Outside ±40% / ±40mg/dL |
|---|---|---|---|---|---|---|
| **Overall** | 5772 | 82.1 | 91.0 | 97.8 | 99.3 | 0.7 |
| **40-50** | 38 | 44.7 | 57.9 | 81.6 | 94.7 | 5.3 |
| **51-80** | 461 | 72.2 | 81.1 | 92.0 | 97.6 | 2.4 |
| **81-180** | 3236 | 82.9 | 91.2 | 97.9 | 99.3 | 0.7 |
| **181-300** | 1799 | 84.9 | 93.6 | 99.2 | 99.7 | 0.3 |
| **301-400** | 226 | 77.0 | 95.1 | 99.6 | 99.6 | 0.4 |
| **401-500** | 12 | 58.3 | 75.0 | 100.0 | 100.0 | 0.0 |

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- **Medtronic Guardian Sensor 3 label** as part of original MiniMed 670G approval - does not include recent arm-wear indication, and uses twice-daily calibration data:

**Table 3.** Agreement (%) of SG-YSI paired points within YSI glucose ranges; Calibration every 12 hours.

| YSI glucose ranges (mg/dL) | Number of paired SG-YSI | Percent of SG within 15/15% of YSI | Percent of SG within 20/20% of YSI | Percent of SG within 30/30% of YSI | Percent of SG within 40/40% of YSI | Percent of SG greater than 40/40% of YSI |
|---|---|---|---|---|---|---|
| Overall | 12090 | 78.8 | 88.2 | **96.1** | 98.9 | 1.1 |
| <40* | 12 | 41.7 | 66.7 | 100 | 100 | 0 |
| ≥40-60* | 353 | 87.3 | 96.9 | 99.2 | 100 | 0 |
| >60-80* | 1445 | 77.9 | 88.4 | 98.3 | 99.7 | 0.3 |
| >80-180 | 6505 | 78.6 | 87.2 | 95.3 | 98.6 | 1.4 |
| >180-300 | 3277 | 79 | 89.1 | 96.2 | 98.9 | 1.1 |
| >300-350 | 366 | 79.5 | 88.5 | 95.9 | 100 | 0 |
| >350-400 | 117 | 76.9 | 91.5 | 98.3 | 100 | 0 |

- **Dexcom G5 label** - accuracy data starts on page 301

**Table 1-A. System Agreement to YSI Within CGM Glucose Ranges (Adult)**

| CGM Glucose Range[1] (mg/dL) | Study[2] | Number of Paired CGM-YSI | Percent Within 15/15% YSI | Percent Within 20/20% YSI | Percent Within 30/30% YSI | Percent Greater Than 40/40% YSI |
|---|---|---|---|---|---|---|
| Overall | Original | 9152 | 71% | 82% | 92% | 3% |
| | Software 505 | 2263 | 86% | 93% | 98% | 1% |
| 40-60 | Original | 512 | 67% | 78% | 88% | 6% |
| | Software 505 | 120 | 89% | 94% | 98% | 0% |
| 61-80 | Original | 781 | 73% | 85% | 94% | 2% |
| | Software 505 | 226 | 91% | 96% | 99% | 0% |
| 81-180 | Original | 3853 | 67% | 78% | 91% | 3% |
| | Software 505 | 738 | 84% | 92% | 98% | 1% |
| 181-300 | Original | 2784 | 72% | 84% | 93% | 4% |
| | Software 505 | 798 | 86% | 93% | 98% | 1% |
| 301-350 | Original | 775 | 82% | 91% | 97% | 2% |
| | Software 505 | 229 | 86% | 94% | 98% | 1% |
| 351-400 | Original | 447 | 74% | 84% | 91% | 5% |
| | Software 505 | 152 | 80% | 92% | 97% | 0% |

*[1]CGM readings are within 40-400 mg/dL, inclusive.*

*[2]Both sets of study data are presented and are labeled as Original (SW10050) or Software 505 Study (SW10505).*

- **Senseonics Eversense label**, per FDA Advisory Committee Meeting briefing materials last week - see here for PRECISE II data (first picture) and here for PRECISION data (second picture). Both include the improved algorithm.

**Table 1** - CGM System agreement to YSI organized by CGM glucose ranges; data pooled from accuracy assessments on **days 1, 30, 60, and 90** of the PRECISE II clinical study, analyzed using SW-602 algorithm

| CGM Glucose Range (mg/dL) | Number of Paired CGM and YSI Reference | Percent of CGM System Readings Within | | | | |
|---|---|---|---|---|---|---|
| | | Percent 15/15% of Reference | Percent 20/20% of Reference | Percent 30/30% of Reference | Percent 40/40% of Reference | Percent Greater than 40/40% of Reference |
| Overall | 15753 | 86.8 | 94.3 | 98.6 | 99.6 | 0.4 |
| 40 - 60 | 480 | 85.4 | 92.1 | 97.7 | 99.6 | 0.4 |
| 61 - 80 | 1111 | 83.3 | 90.7 | 97.4 | 99.1 | 0.9 |
| 81 - 180 | 7844 | 85.6 | 93.5 | 98.3 | 99.6 | 0.4 |
| 181 - 300 | 5377 | 88.3 | 95.6 | 99.1 | 99.7 | 0.3 |
| 301 - 350 | 692 | 90.8 | 98.0 | 99.7 | 99.9 | 0.1 |
| 351 - 400 | 249 | 96.8 | 99.2 | 100.0 | 100.0 | 0.0 |

**Table 1** - CGM System agreement to YSI organized by CGM glucose ranges; PRECISION study, **all days**, analyzed using SW-602 algorithm

| CGM Glucose Range (mg/dL) | Number of Paired CGM and YSI Reference | Percent of CGM System Readings Within | | | | |
|---|---|---|---|---|---|---|
| | | Percent 15/15% of Reference | Percent 20/20% of Reference | Percent 30/30% of Reference | Percent 40/40% of Reference | Percent Greater than 40/40% of Reference |
| Overall | 15170 | 85.4% | 92.8% | 98.1% | 99.3% | 0.7% |
| 40 - 60 | 1236 | 91.9% | 96.0% | 98.4% | 99.3% | 0.7% |
| 61 - 80 | 2003 | 87.3% | 94.1% | 99.1% | 99.6% | 0.4% |
| 81 - 180 | 5786 | 80.5% | 89.9% | 97.2% | 99.0% | 1.0% |
| 181 - 300 | 3566 | 84.8% | 92.8% | 98.1% | 99.2% | 0.8% |
| 301 - 350 | 1628 | 92.8% | 97.5% | 99.1% | 99.9% | 0.1% |
| 351 - 400 | 951 | 91.5% | 95.8% | 98.6% | 99.8% | 0.2% |

## Additional Special Controls, Including Rate-of-Change and Interoperability

- **Mandatory shutoff:** The device must include appropriate measures to ensure that disposable sensors cannot be used beyond its claimed sensor wear period.
- **Transmission:** Design verification and validation must include a detailed strategy to ensure secure and reliable means of iCGM data transmission to provide real-time glucose readings at clinically meaningful time intervals to devices intended to receive the iCGM glucose data.
- **Rate-of-change (1):** There shall be no more than 1% of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dl/min when the corresponding true negative glucose rate of change is less than -2 mg/dl/min as determined by the corresponding blood glucose measurements.
- **Rate-of-change (2):** There shall be no more than 1% of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dl/min when the corresponding true positive glucose rate of change is greater than 2 mg/dl/min as determined by the corresponding blood glucose measurements.

- **Pediatric:** Data demonstrating similar accuracy and rate of change performance of the iCGM in the pediatric population as compared to that in the adult population, or alternatively a clinical and/or technical justification for why pediatric data are not needed, must be provided and determined by FDA to be acceptable and appropriate.
- **Gaps:** Data must demonstrate that throughout the claimed sensor life, the device does not allow clinically significant gaps in sensor data availability that would prevent any digitally connected devices from achieving their intended use
- **Consistency over wear time:** Clinical study results must demonstrate consistent analytical and clinical performance throughout the sensor wear period.
- **Manufacturing:** Design verification and validation must include adequate controls established during manufacturing and at product release to ensure the released product meets the performance specifications as defined in paragraphs (1) and (2) of this section.
- **Interference:** The device must demonstrate clinically acceptable performance in the presence of clinically relevant levels of potential interfering substances that are reasonably present in the intended use population, including but not limited to endogenous substances and metabolites, foods, dietary supplements, and medications
- **Human factors:** Design verification and validation must include results obtained through a usability study that. demonstrates that the intended user can use the device safely and obtain the expected glucose measurement accuracy.
- **Transparent Accuracy Labeling:** Must include a separate description of the following sensor performance data observed in the clinical study performed in conformance with paragraph (1) for each intended use population, in addition to separate sensor performance data for each different iCGM insertion or use sites (e.g., abdomen, arm, buttock):
    - A description of the accuracy in the following blood glucose concentration ranges: less than 54 mg/dL, 54-70 mg/dL, 70-180 mg/dL, 180-250 mg/dL, and greater than 250 mg/dL
    - A description of the accuracy of positive and negative rate of change data.
    - A description of the frequency and duration of gaps in sensor data.
    - A description of the true, false, missed, and correct alert rates and a description of the available glucose concentration alert settings if applicable.
    - A description of the observed duration of iCGM life for the device.
- **Dr Lias highlighted that the labeling above is also key to the "integrated CGM" piece**. If devices want to connect with an iCGM seamlessly, they must understand the performance ("transparency of performance specifications"). Clear labeling will certainly help on this front!

## Thoughts from Key Opinion Leaders on the FDA's New iCGM Pathway, Interoperability, and Dexcom's G6

### Dr. Daniel DeSalvo - "Huge, forward-thinking move by the FDA," a "new era" with accurate, factory-cal sensors in an interoperable ecosystem

This was a huge, forward-thinking move by the FDA that will pave the way for faster innovation and interoperability of the Dexcom G6 CGM while maintaining optimal patient safety. We are embarking on a new era in diabetes care with the advent of automated insulin delivery systems, smart pens, watches, and wearables pairing with highly accurate, factory-calibrated sensors in an interoperable diabetes device ecosystem. People with diabetes stand to benefit as treatment choices become more widely available, the burden of diabetes management is lifted with increasing automation, and clinical outcomes improve.

The "special controls" for integrated CGMs set forth by the FDA to ensure safety, efficacy, and interoperability set a very high bar for CGM systems. While the iCGM designation provides an immediate benefit to the Dexcom G6 in easing the regulatory pathway for system innovation and inoperability, I am hopeful that the newly established iCGM standards will lead to enhanced accuracy and performance of future CGM devices from other manufacturers. The competitive moat is indeed high, but could very well lead to the development of multiple CGM systems that will be integral to the diabetes device ecosystem of the future - one that ideally will offer a wide range of choices for patients and providers. - Dr. Daniel DeSalvo, Baylor College of Medicine

### Dr. Henry Anhalt - Interoperability has now been "legitimized by the FDA" in many respects, "deeply supportive of mandatory shutoff"

"Clearly FDA has moved swiftly to recognize that SMBG has fallen short of expectations, not only in terms of accuracy, but in terms of utility in the management of patients with diabetes. This dovetails nicely with the understanding that time-in-range and other outcome measures provide far more value than A1c alone.

Interoperability has been one of the rallying cries of the diabetes community for years, and now has been, in many respects, legitimized by the FDA through its current guidance.

It would be great to see the 510(k) pathway for iCGM spill over to AID systems; however, I doubt that will happen given the current classification of AID systems and the FDA's historical approach to see systems in totality rather than individual components.

I am deeply supportive of mandatory shutoff, if in fact, this results in more accurate and safer use of CGM. However, I'm not necessarily supportive of continuous communication of readings - for example, Abbott's FreeStyle Libre (flash) clearly benefits large swaths of patients.

Lastly, my deep concern is that guidance that results in such an overwhelmingly strong competitive advantage to one company over another may lead to the circumstance, "Whatever doesn't kill us may weaken us beyond the capacity to recover." - Dr. Henry Anhalt, Science37

### Dr. Roy Beck - "Major step forward for CGM" , accuracy benchmarks "appear reasonable", use of confidence intervals "really important"

"This is an important and major step forward for CGM. It is particularly important for systems that will use iCGM to make it easier to adopt newer generations of sensors in systems without having to conduct an extensive clinical study as a new system - something that would be nearly impossible to do.

The accuracy benchmarks appear reasonable and use of the lower-end of the confidence interval is reasonable. Confidence intervals are really important, as your report on my talk at the Endocrine Society Fellows meeting highlighted, but clinicians just tend to think about the point estimate from a study - whether it be accuracy of a sensor or the improvement with a drug or device - and not about the confidence interval which is much more informative." - Dr. Roy Beck, Jaeb Center for Health Research

### Dr. Zan Fleming - "FDA has set a high bar for all CGM products, while counter-intuitively down-grading the regulatory class"

"FDA has effectively set a high bar for all CGM products, while counter-intuitively down-grading the regulatory class - at least for high-performing systems.

The interoperability provision is amazing. It has implications for devices and apps beyond the CGM segment or even the diabetes space. I am very optimistic that FDA is embracing interoperability and even pushing for it. No doubt this is a major game-changer for CGM and beyond.

In the short run, a very large competitive moat has been put up against other companies. Longer term, the competitors have to catch up - and that is a good thing for people living with diabetes." - Dr. Zan Fleming, Kinexum

### Dr. Bruce Buckingham - "Great news for the field...much easier to use sensor data with multiple different platforms"

"This is great news for the field. As a class II device it should now be much easier to use sensor data with multiple different platforms and devices.

What is not included in the tables (above) is the sensor function on day 1 compared to day 7 or 10. I think there may still be some issue with maintaining this level of accuracy on day 1 due to local tissue trauma at the time of insertion. I am also a little concerned about sensor function on the last days of sensor life.

The FDA did not specifically state the number of lot numbers that would need to be tested, but I think they generally request a minimal number of 3-5 lot numbers (I do not know the details).

The question of "significant" gaps probably needs to be defined by the system using the CGM data. Connected pens may tolerate a longer data gap than hybrid closed-loop, or particularly a full-closed loop system.

The condition to have secure CGM transmission probably means some level of data encryption, which would probably mean that completely open-source availability of the data would not be possible and might always require some agreement with the sensor manufacturer to get the data." - Dr. Bruce Buckingham, Stanford University

## How does the FDA define an iCGM?

**"FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Dexcom G6 Continuous Glucose Monitoring System, and substantially equivalent devices of this generic type, into Class II under the generic name** "Integrated continuous glucose monitoring system." FDA identifies this generic type of device as: Integrated continuous glucose monitoring system. An integrated continuous glucose monitoring system (iCGM) is intended to automatically measure glucose in bodily fluids continuously or frequently for a specified period of time. iCGM systems are designed to reliably and securely transmit glucose measurement data to digitally connected devices, including automated insulin dosing systems, and are intended to be used alone or in conjunction with these digitally connected medical devices for the purpose of managing a disease or condition related to glycemic control.

**Regulatory Class:** Class II (510(k) clearance)

**Product Code:** QBJ

## Dexcom's G6 Indications for Use

**"The Dexcom G6 Continuous Glucose Monitoring System (Dexcom G6 System) is a real time, continuous glucose monitoring device indicated for the management of diabetes in persons age 2 years and older.** The Dexcom G6 System is intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G6 System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6 System also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. The Dexcom G6 System is also intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. The Dexcom G6 System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes."

*--by Adam Brown and Kelly Close*