

July 15, 2016

SUBMITTED VIA ELECTRONIC DELIVERY to patricio.garcia@fda.hhs.gov

Mr. Patricio Garcia
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Bldg. 66, rm. 1116
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Silver Spring, MD 20993

**RE: Docket No. FDA-2016-N-0001
Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory
Committee July 21st Meeting**

Dear Mr. Garcia:

JDRF is pleased to provide comments on the issue to be discussed by the committee on July 21, 2016, regarding “a premarket approval application (PMA) panel-track supplement for a proposed change in intended use of Dexcom, Inc.’s, Dexcom G5[®] Mobile Continuous Glucose Monitoring System (CGM) device so that, in addition to tracking and trending interstitial fluid glucose concentrations, patients can use the device as a replacement for their blood glucose meters and make treatment decisions based on the interstitial fluid glucose concentration reported by the CGM.”

I. Introduction

JDRF is the leading global charitable funder of type 1 diabetes (T1D) research, with a mission to accelerate life-changing breakthroughs to cure, prevent and treat T1D and its complications. Founded in 1970 by parents of children with T1D, JDRF has invested nearly \$2 billion in research since its inception and employs over 20 scientists to manage its research portfolio, including significant work to improve glucose control.

Despite advances in diabetes care, there is much room for improvement in glucose control, according to the most recent data from the T1D Exchange registry. These data show that less than one third of adults and only one fifth of children in the United States meet recommended glycemic targets as measured by glycated hemoglobin or hemoglobin A1c (HbA1c). They also show that rates of severe hypoglycemia and diabetic ketoacidosis (DKA), which can be life-threatening diabetes complications, remain unacceptably high.¹

¹ Miller KM, Foster NC, Beck RW, et al. Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data from the T1D Exchange Clinic Registry. *Diabetes Care* 2015; 38:971-978.

JDRF's comments below provide evidence from numerous studies to conclude that people with T1D have better outcomes from CGM use, that CGM users are currently relying on CGM data for treatment decisions, that those using CGM for treatment decisions have significantly better outcomes than those who use SMBG alone, that researchers have found that DexCom G5[®] has a level of accuracy adequate for use in treatment decisions, and that SMBG labels provide support for updating the CGM label.

Despite the overwhelming evidence that people who use CGM achieve better outcomes, only 11% of people with T1D in the United States currently take advantage of this technology.² Current FDA labeling is a barrier to adoption of CGM. For example, the Centers for Medicare & Medicaid Services (CMS) uses the current label language as a reason to deny coverage for CGM devices. Current labeling is also a barrier to proper training of patients on how to effectively utilize features of the CGM to maximize the benefit of the device.

JDRF urges the advisory committee to support and the FDA to approve the proposed change in intended use and allow patients to use the device as a replacement for their blood glucose meters in making treatment decisions.

II. Randomized Control Trials Show Better Outcomes from CGM Use

The benefits of CGM devices have been proven in multiple studies comparing outcomes of CGM users and non-CGM users. JDRF independently funded a landmark trial to evaluate the efficacy of adding real-time CGM to intensive insulin therapy. The trial demonstrated that regular use of CGM results in significant improvements in all measures of glycemic control without increasing hypoglycemia.^{3,4}

Moreover, a meta-analysis conducted by the Agency for Healthcare Research and Quality (AHRQ) illustrated that CGM is superior to self-monitoring of blood glucose (SMBG) alone in lowering HbA1c without affecting the risk of severe hypoglycemia in individuals with T1D.⁵

² Miller KM, Foster NC, Beck RW, et al. Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data from the T1D Exchange Clinic Registry. *Diabetes Care*. 2015; 38:971-978.

³ Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW et al. Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes. *N Engl J Med*. 2008;359(14):1464-76.

⁴ Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Beck RW, Buckingham B, Miller K, et al. Factors Predictive of Use and Benefit from Continuous Glucose Monitoring in Type 1 Diabetes. *Diabetes Care*. 2009; 32(11):1947-53.

⁵ Golden SH, Sapir T. Methods for Insulin Delivery and Glucose Monitoring in Diabetes: Summary of a Comparative Effectiveness Review. *J Manag Care Pharm*. 2012;18(6 Suppl):S1-17.

More recent studies have demonstrated the ways in which advancements in technology have resulted in improved health outcomes. When looking at longer-term outcomes, one study found that the “proportion of participants with Hemoglobin A1c (HbA1c) reductions $\geq 0.5\%$ was higher” in individuals with T1D who used CGM versus those who did not.⁶ Furthermore, CGM use has been shown to reduce HbA1c levels by 0.9% in multiple daily injections (MDI) users who are not currently at glycemic target.⁷

Thus, overall health outcomes are improved by use of CGM.

III. Studies Show CGM Users are Currently Relying on CGM Data for Treatment Decisions and Users Doing So Have Significantly Better Outcomes

As the sensors in CGM devices have evolved and their accuracy improved, users have become more reliant on the readings. Several studies have shown that individuals’ increased level of comfort with the data reported by CGMs has led to a simultaneous decrease in utilization of SMBG, not only for monitoring of glucose values, but also for determining treatment.

In a survey of 222 individuals with T1D, 89 percent of respondents stated that they used the “rate-of-change” arrows on their CGM device to make their insulin dosing decisions.⁸

Moreover, two recent trials found that individuals using CGM had both reduced SMBG use and improved outcomes. One randomized trial, reported in June 2016, found that individuals using CGM reduced their daily SMBG tests from 5.1 tests per day to 3.6 tests per day and lowered their HbA1c by 0.9%.⁹

A study published in 2015 found that after one year of CGM use, “almost daily” CGM users reduced daily use of SMBG by more than half (from 6.8 tests per day to 3.2 tests per day) while concurrently experiencing an 86 percent reduction in the number of events requiring emergency medical treatment compared to the year prior when not using CGM.¹⁰

Thus, studies show CGM users are currently relying on CGM data for treatment decisions and that users doing so have good outcomes.

⁶ New, J.P., et al. Continuous Glucose Monitoring in People with Diabetes: the Randomized Controlled Glucose Level Awareness in Diabetes Study (GLADIS). *DIABETICMedicine*. 3 February 2015.

⁷ Dagens Diabetes. Diabetes Technology Highlights - Dexcom Diamond Study. 20 June 2016. <http://www.dagensdiabetes.info/index.php/alla-senaste-nyheter/2266-ada-diamond-study-cgm-g4-versus-mdi-6-mol-mol-benefit-61-more-min-in-glucose-range-day>.

⁸ Pettus J. et al. How Patients with Type 1 Diabetes Translate Continuous Glucose Monitoring Data into Diabetes Management Decisions. *Endocr Pract.* June 2015, Vol. 21, No. 6, pp. 613-620.

⁹ Dagens Diabetes. Diabetes Technology Highlights - Dexcom Diamond Study. 20 June 2016. <http://www.dagensdiabetes.info/index.php/alla-senaste-nyheter/2266-ada-diamond-study-cgm-g4-versus-mdi-6-mol-mol-benefit-61-more-min-in-glucose-range-day>.

¹⁰ Chamberlain, James, et al. Impact of Frequent and Persistent Use of Continuous Glucose Monitoring (CGM) on Hypoglycemia Fear, Frequency of Emergency Medical Treatment, and SMBG Frequency After One Year. *Journal of Diabetes Science and Technology* 1-6. 2015.

IV. DexCom CGM Meets Standards Developed by Independent Researchers for CGM Use in Treatment Decisions

In a recent study published in *Diabetes Technology & Therapeutics*,¹¹ researchers utilized clinical data and a model of T1D to evaluate error rates of CGM and their potential effect in using CGM to make treatment decisions. The study utilized an in silico model of T1D which has been accepted by FDA¹² for approximation of human glucose/insulin utilization, interstitial sensor performance, and subcutaneous insulin delivery. The study combined that FDA accepted model with clinical data of CGM, insulin pump, SMBG and meal bolus data. It utilized a statistical measure known as mean absolute relative difference, or MARD.

After analyzing the data, the study found that “using CGM for insulin dosing decisions is feasible below a certain level of sensor error, estimated in silico at MARD = 10 percent.” The Dexcom G5[®] Mobile CGM System meets this standard. On October 21, 2014, the FDA approved a modification of the algorithm for the previously approved Dexcom G4 PLATINUM CGM System. The algorithm modification referred to as Software 505 improved the sensor accuracy. The PMA supplement (P120005/S018) indicates that with Software 505 the sensor MARD on day of wear 1, 4, and 7 was 10.7 percent, 8.0 percent, and 8.5 percent, respectively.¹³ The sensor and algorithm used in the Dexcom G5[®] Mobile CGM System is the same as the sensor and algorithm approved in the Dexcom G4 PLATINUM CGM PMA supplement P12005 S018.

V. Review of SMBG Labels Support Change in CGM Label

The current indication for the Dexcom G5[®] CGM says:

“The Dexcom G5 Mobile Continuous Glucose Monitoring System is a glucose monitoring system indicated for detecting trends and tracking patterns in persons (age 2 and older) with diabetes. The system is intended for single patient use and requires a prescription. The Dexcom G5 Mobile System is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home glucose monitoring devices. The Dexcom G5 Mobile System aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments, which may minimize these excursions. Interpretation of the Dexcom G5 Mobile System results should be based on the trends and patterns seen with several sequential readings over time.”¹⁴

¹¹ Kovatchev, B., et al. Assessing Sensor Accuracy for Non-Adjunct Use of Continuous Glucose Monitoring. *Diabetes Technology & Therapeutics*. 17; 3 November 2015.

¹² U.S. Food and Drug Administration. Device Master File MAF-1521. February 10, 2008.

¹³ U.S. Food and Drug Administration. PMA Supplement P120005/S018. Summary of Safety and Effectiveness Data. October 21, 2014. http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S018B.pdf.

¹⁴ U.S. Food and Drug Administration. Dexcom G5 Mobile Continuous Glucose Monitoring Device Premarket Approval (PMA). August 19, 2015. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P120005S033>.

A review of the indications for self-monitoring of blood glucose (SMBG) devices supports a change to this CGM indication. In the last ten years, FDA’s cleared indications for SMBG systems have commonly included the following indications:

“The XX Blood Glucose Monitoring System is intended to be used for the quantitative measurement of glucose....by health care professionals and people with diabetes at home as an aid to monitor the effectiveness of diabetes control.”¹⁵

“The XXX Blood Glucose Test Systems are used for self-monitoring of blood glucose as an adjunct to the care of person with diabetes.”¹⁶

As detailed in sections II, III, and IV above, research clearly shows that CGMs are able to fulfill these functions, to provide quantitative measurement of glucose, act as an aid to monitor the effectiveness of diabetes control, and serve as an adjunct to the care of the person with diabetes.

Moreover, the CGM devices available today have vastly better accuracy levels than SMBG systems did when they were first approved with these indications. For example, an analysis found levels of mean absolute relative difference, or MARD, for SMBG systems in the 1990s to be significantly over 10 percent,¹⁷ far higher than the rates for the approved Dexcom G5® system.¹⁸

Thus, there is no need for the CGM indication to continue to include outdated language that CGM should “complement, not replace, information obtained from standard home glucose monitoring devices.”

VI. Conclusion: JDRF Recommends Change in CGM Intended Use Be Approved

As a result of this review of the evidence, JDRF urges the advisory committee to support and the FDA to approve the proposed change in intended use of the Dexcom G5® Mobile Continuous Glucose Monitoring System device so that, in addition to tracking and trending interstitial fluid glucose concentrations, patients can use the device as a replacement for their blood glucose meters and make treatment decisions based on the interstitial fluid glucose concentration reported by the CGM.

¹⁵ U.S. Food and Drug Administration. Summary of 510(K) safety and effectiveness information. January 14, 2000. http://www.accessdata.fda.gov/cdrh_docs/pdf/K992684.pdf.

¹⁶ U.S. Food and Drug Administration. Summary of 510(K) safety and effectiveness information. February 26, 1999. http://www.accessdata.fda.gov/cdrh_docs/pdf/K990649.pdf.

¹⁷ Bohme, Philip, et al. Evolution of Analytical Performance in Portable Glucose Meters in the Last Decade. *Diabetes Care* 26:1170–1175, 2003.

¹⁸ U.S. Food and Drug Administration. Summary of Safety and Effectiveness Data. October 21, 2014. http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S018B.pdf.

JDRF is committed to accelerating life-changing breakthroughs to cure, prevent, and treat T1D and its complications. JDRF appreciates the opportunity to submit comments to the advisory committee on this matter and applauds the FDA's efforts to improve public health outcomes of people with T1D.

Thank you for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read 'Aaron Kowalski', written in a cursive style.

Aaron Kowalski, Ph.D.
Chief Mission Officer and Vice President, Research
JDRF