Journal of Diabetes Science and Technology
Volume 1, Issue 1, January 2007

CONTROVERSIES in
Continuous Glucose Monitoring

The Need for Performance Standards for Continuous Glucose Monitors

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Abstract

Self-monitoring blood glucose (SMBG) devices or glucose meters currently provide a means for patients to manage insulin dosing through intermittent monitoring of blood glucose levels several times a day, but newer continuous glucose monitor devices (CGM) offer the potential of real-time glucose monitoring with less pain and lower cost. Unlike SMBG devices that sample glucose levels in circulating blood, CGM samples from the interstitial fluid. CGM devices generate not only a single level, but through averaging with past glucose results, can predict future trends. While consensus guidelines exist for evaluating the agreement of SMBG devices to other glucose and laboratory methods, no guidelines currently exists for CGM devices. Standards are needed to define the performance of CGM devices, both in terms of spot accuracy and trend information, as well as the level of performance required for clinical management. The Diabetes Technology Society (DTS) has been in close communication on the development of CGM guidelines with the Food and Drug Administration (FDA) and the Clinical and Laboratory Standards Institute (CLSI). Development of standards for CGM devices if adopted by the FDA would set minimum requirements of performance for manufacturers to meet in producing CGM devices and define common terminology for the display and clinical utilization of CGM data. It is expected that CGM performance standards will advance over time as technology improves and consumer demands change. The development of CGM standards will also play an important role in accelerating the development of an artificial pancreas, which relies on CGM technology.

J Diabetes Sci Technol 2007; 1:92-94

The use of self-management blood glucose (SMBG) devices or glucose meters has helped patients with type 1 and type 2 diabetes achieve more normal glucose levels and lower risk of cardiovascular and long-term complications. Patients utilize SMBG devices to self-manage their insulin dosing by testing blood glucose levels one to four or more times a day. Despite the ease of use of SMBG devices, many people with diabetes are not compliant with testing at the frequency recommended by their physician because of the cost of testing supplies and the pain of repeated fingersticks.

Continuous glucose monitors (CGM) are medical devices that measure glucose in a more real-time manner. Currently marketed CGM devices are attached to the skin by an adhesive patch and can be worn for up to several days. CGM offers patients the potential of monitoring their glucose levels and managing insulin dosages without the necessity of repeated fingersticks. CGM devices can provide real-time readings to the wearer, which allow for an immediate response, such as a supplemental dose of insulin, a snack, or a period of exercise. Unlike SMBG devices that sample glucose levels in capillary, arterial or

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Abbreviations: (CGM) continuous glucose monitor, (CLSI) Clinical and Laboratory Standards Institute, (DTS) Diabetes Technology Society, (FDA) Food and Drug Administration, (SMBG) self-monitoring blood glucose

Key Words: FDA, glucose, guidelines, monitor, standards

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venous blood, CGM measures the glucose concentration in the interstitial fluid just under the skin. Circulating blood glucose equilibrates with the interstitial fluid compartment which bathes cells that require glucose for energy. Interstitial fluid glucose levels thus lag behind blood glucose levels by the amount of time that is required for glucose to diffuse from the circulatory system into interstitial fluid. This lag time may be as little as a few minutes or as much as 10-20 minutes. The exact duration of the lag depends on whether the blood glucose level is rising, stable, or falling, and the type of sensor making the measurement. Interstitial fluid glucose levels, compared to blood levels, may be more reflective of the amount of glucose available for cellular metabolism.

Although CGM is called continuous, CGM devices actually sample interstitial fluid glucose intermittently, with a testing frequency ranging from every few seconds to several minutes between measurements. The measurements are averaged and presented as a single reading every few minutes to quarter hour. Software within the CGM devices can combine current levels with previous results to predict a future trend and direction of glucose change. CGM can thus display not only a single glucose result, but also the direction of glucose change (up, down, or stable), as well as the magnitude of change (the difference between glucose concentration per time interval). Because CGM presents current levels of glycemia along with trend information, this technology offers the potential to predict hypoglycemic events before they occur and describe patterns of glucose variability that may not be detectable from utilizing SMBG devices that intermittently sample blood only a few times per day.

While guidelines exist for comparing SMBG devices to laboratory methodologies, there is no current consensus on how to compare CGM devices. SMBG accuracy can be evaluated by considering the differences between finger prick capillary blood, tested with the SMBG device, and venous blood levels, analyzed in a laboratory setting, when the samples are collected at the same time. Yet, there is no current definition of good agreement for CGM devices given the time lag between blood and interstitial fluid levels, or even how to display and interpret the data produced by CGM in a common fashion. Development of a guideline for CGM devices would address these issues by reaching consensus on how CGM data should be presented and compared between devices and different laboratory and SMBG glucose methodologies. Terminology would be defined for interstitial fluid glucose and its relationship to blood glucose levels, and defining the degree of agreement for acceptable technical performance would allow assessment of method comparability. Finally, a guideline for CGM would present recommendations for clinical interpretation of CGM data for utilization in patient care.

The Diabetes Technology Society (DTS) is a nonprofit organization, based in Foster City, California, devoted to the development of technology to help people with diabetes. A major goal of this organization is to bring about the creation of an artificial pancreas. An artificial pancreas would measure glucose levels continuously and automatically, and based upon embedded control software utilize a pump device to deliver an appropriate variable dose of insulin by way of an indwelling catheter.

One of the biggest barriers to development of an artificial pancreas system is the difficulty companies are having in obtaining FDA approval for new continuous glucose sensors. These sensors could be used as components of an artificial pancreas system. At this time, every continuous glucose sensor that is developed provides a string of point measurements, but these measurements are far less accurate than the intermittent sampling SMBG devices already approved by the FDA. Continuous sensors, however, also provide trend information which allows prediction of future glucose levels that the intermittent SMBG devices cannot provide. There is an overwhelming concurrence in the glucose monitoring industry that if performance standards for continuous glucose monitors can be developed and adopted by the FDA and other standards-development organizations, the engineers will know how to develop products to meet the standards, and the FDA will have a basis for approving continuous glucose monitors. What is needed are statistical measures that define the performance of these monitors, both in terms of point accuracy and trend information, as well as a defined level of performance that will meet the requirements of clinical management. It is expected that the first consensus standard will become the minimum level of required performance and that over time this standard will have to improve as sensor technologies improve.

DTS has been in close communication on the development of a CGM device guideline with the FDA and Clinical and Laboratory Standards Institute (CLSI) based in Wayne, Pennsylvania. CLSI is a global, nonprofit, standards-developing organization that promotes the development and use of voluntary consensus standards and guidelines within the healthcare community. Formerly known as the National Committee on Clinical Laboratory Standards (NCCLS), the organization recently changed its name to CLSI to become more globally engaged. CLSI's mission is "to enhance the value of medical testing and health care services through the development of standards, guidelines, and best practices" in order to facilitate better, safer, and more cost effective patient care worldwide. A consensus standard or guideline is a document developed using the principles of the consensus process, to promote uniform

products, materials, methods, or practices. CLSI is based on the principle that consensus is an efficient and cost-effective way to improve patient testing and services.

The purpose of developing performance standards and guidelines for CGM is to provide an objective means of evaluating data generated by these devices. Standards lay out specifications and criteria to be applied consistently in the classification of materials, in the manufacture and supply of products, in testing and analysis, in terminology and in the provision of services to provide a reference framework, or a common technological language between manufacturers and customers. When new technologies or business sectors emerge, standards on basic features, such as terminology, compatibility and interoperability, help to disseminate the technology and increase the size of the market for products and services. Agreement on test methods allows meaningful comparison of products. A standard must be followed exactly as written, whereas a guideline may be modified by the user. A standard contains verbs such as will, must, and shall, whereas a guideline contains verbs such as should, could, may, or might. Development of standards and guidelines is a pragmatic method of engaging the diabetes technology community from industry, academia, and government to define the minimum necessary analytical and clinical performance of CGM devices. A potential disadvantage of establishing standards and guidelines are that companies might be discouraged from improving performance beyond minimum defined criteria. Also, to be effective, standards and guidelines must be revised frequently in response to rapidly changing technologies and consumer demands. Standardization of performance of CGM will ensure that patients' needs are met, and also allow individual manufacturers the freedom to design their own solutions for meeting those needs.

DTS presented the DTS International Panel for establishment of Performance Standards for Continuous Glucose Monitors in November, 2005 in San Francisco. Carol Herman, the FDA Director of Standards, was the moderator and David Klonoff from DTS was Chair. This panel included 30 scientists and clinicians interested in continuous glucose monitoring. Members and observers at the meeting represented industry, government, academia, non-profit organizations, and patients. Participating US government agencies included FDA, NIH, CDC, and the US Army. Participating organizations included DTS, CLSI, American Diabetes Association, Juvenile Diabetes Research Foundation, and the International, and Human Factors and Ergonomics Society. The product of this Panel was a scope of work that includes definitions and methods for determining analytical and clinical metrics for continuous interstitial glucose monitoring.

DTS then formally applied to CLSI to supervise the creation of performance guidelines for CGM technology. In April, 2006, at a national meeting in Falls Church, Virginia, the CLSI Chairholders Council agreed to work cooperatively with DTS on the development of a consensus guideline for continuous glucose monitoring. The CLSI Subcommittee on Continuous Glucose Monitoring (within the CLSI Point of Care Area Committee) was formed. This subcommittee met for the first time in San Francisco in July, 2006 and further meetings are planned in order to complete a set of recommenced guidelines for describing CGM performance. Although the FDA is not obligated to accept the Subcommittee's recommendations as either guidelines or as standards, FDA officials have expressed great interest in this initiative, and they appear favorably inclined to these efforts. If the FDA does accept the Subcommittee's recommendations for use in the United States, then it is possible that at a later date the International Organization for Standardization (ISO), based in Geneva, Switzerland will also accept the recommendations coming out of this CLSI-sponsored initiative. ISO is a non-governmental organization or federation of the national standards bodies of 157 countries.

Over time, it is expected that CGM performance standards will become tighter, but every process must begin somewhere, and a process of developing standards for CGM is now established. Once these standards are in place, it will be easier and more efficient for industry to develop their continuous glucose monitoring products, because industry scientists will know what level of performance to aim for and how to best describe the performance. This knowledge will lead to savings of time and money during the development process. In that case, DTS and CLSI together will have played an important role in accelerating the development of an artificial pancreas by assisting industry to create better continuous glucose monitoring products.

Acknowledgements:

The authors thank David Sterry, M.T. (ASCP), Standards Administrator, Clinical and Laboratory Standards Institute, Wayne, PA, for his guidance with terminology for this article.