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MEETING PROCEEDINGS

Do Currently Available Blood Glucose Monitors Meet Regulatory Standards? 1-Day Public Meeting in Arlington, Virginia

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Abstract

Blood glucose monitors (BGMs) are approved by regulatory agencies based on their performance during strict testing conducted by their manufacturers. However, after approval, there is uncertainty whether BGMs maintain the accuracy levels that were achieved in the initial data. The availability of inaccurate BGM systems pose a public health problem because their readings serve as a basis for treatment decisions that can be incorrect. Several articles have concluded that BGMs in the marketplace may not consistently provide accurate results in accordance with the regulatory standards that led to approval. To address this growing concern, Diabetes Technology Society organized and conducted a 1-day public meeting on May 21, 2013, in Arlington, VA, presided by its president, David Klonoff, M.D., FACP, Fellow AIMBE, to determine whether BGMs on the market meet regulatory standards. The meeting consisted of four sessions in which Food and Drug Administration diabetes experts as well as leading academic clinicians and clinical chemists participated: (1) How is BGM performance determined? (2) Do approved BGMs perform according to International Organization for Standardization standards? (3) How do approved BGMs perform when used by patients and health care professionals? (4) What could be the consequence of poor BGM performance?

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Introduction

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To address this growing concern, Diabetes Technology Society organized and conducted a 1-day public meeting on May 21, 2013, in Arlington, VA, presided by its president, David Klonoff, M.D., FACP, Fellow AIMBE, to determine whether BGMs on the market meet regulatory standards. The meeting consisted of four sessions in which Food and Drug Administration (FDA) diabetes experts as well as leading academic clinicians and clinical chemists participated:

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Abbreviations: (BGM) blood glucose monitor, (CE) Communauté Européenne, (CLSI) Clinical and Laboratory Standards Institute, (FDA) Food and Drug Administration, (ICU) intensive care unit, (ISO) International Organization for Standardization, (MDR) medical device report, (MGC) moderate glycemic control, (OTC) over the counter, (POC) point of care, (SMBG) self-monitoring of blood glucose, (TE) total error, (TGC) tight glycemic control

Keywords: accuracy, Arlington, FDA, glucose, meeting, monitor, performance, SMBG

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(1) How is BGM performance determined? (2) Do approved BGMs perform according to International Organization for Standardization (ISO) standards? (3) How do approved BGMs perform when used by patients and health care professionals? (4) What could be the consequence of poor BGM performance?

After welcoming all attendees to the meeting, Dr. Klonoff shared that the mission of the Diabetes Technology Society is to promote development and use of technology to help people with diabetes, and that the BGM is one of the most important technologies used by millions of people worldwide to manage their diabetes. People look to BGMs for accuracy. Dr. Klonoff stated that there are standards already in place for accuracy, with new clinical and analytical standards to be released within the year. This meeting would not be devoted to what the new standards should be, but rather to find out if BGMs maintain their performance after they have been approved. After an increasing number of articles had been published with data showing that, in some cases, BGMs do not meet the standards under which they had been approved, Dr. Klonoff shared that he raised this concern with FDA representatives. They quickly expressed their interest and committed to participating in a 1-day public meeting.

Session 1: How Is Blood Glucose Monitor Performance Determined?

Dr. Klonoff introduced the moderator of session 1, Katherine Serrano, from the Division of Chemistry and Toxicology Devices, Office of In Vitro Diagnostics and Radiological Health, Center for Devices and Radiological Health (CDRH)/FDA, Silver Spring, MD, who called the session to order and introduced the first speaker.

What Are the Current Standards for Blood Glucose Monitor Accuracy? (International Organization for Standardization, Clinical and Laboratory Standards Institute, Food and Drug Administration)

Mitchell G. Scott, Ph.D., a professor of pathology from the Division of Laboratory and Genomic Medicine at Washington University School of Medicine, St. Louis, MO, began his presentation by showing the current standards: American Diabetes Association specifies total analytic error <5% (all values); Clinical Laboratory Improvement Amendments/College of American Pathologists specifies 20% (>60 mg/dl) or 12 mg/dl (<60 mg/dl); ISO 15197/Clinical and Laboratory Standards Institute (CLSI) C-30A2 (published in 2003) specifies that 95% of individual glucose results shall fall within ±15 mg/dl of the results of the reference measurement at glucose concentrations <75 mg/dl and that 95% of individual results shall fall within ±20% at glucose concentrations ≥75 mg/dl; and CLSI POCT12-A3 (published in 2013) specifies ±12.5% (>100 mg/dl), ±12 mg/dl (<100 mg/dl; 95% of values), ±20% (>75 mg/dl), and ±15 mg/dl (<75 mg/dl; 98% of values). Citing data from his laboratory and other published articles, Dr. Scott shared that most of the new BGMs from major manufacturers released in the past 5 years are accurate and precise, with coefficients of variation of less than 4% and a bias less than 3%. In addition, two of the new BGMs correct for extreme hematocrit levels and reducing substances as well as minimize user error with their strip and meter design that require only a small sample volume. Most importantly, even with ISO 15197 under revision and other guidelines for self-monitoring of blood glucose (SMBG) soon to be released, Dr. Scott concluded that, although the standards cannot address user error, he is confident that the BGMs appear to meet new accuracy guidelines in controlled split sample studies.

How Are Blood Glucose Monitors Tested for Approval Including Proper Reference Methods?

Patricia Bernhardt, M.T. (ASCP), a scientific reviewer at the Office of In Vitro Diagnostic Devices and Radiological Health, CDRH/FDA, started by explaining that BGMs are cleared as class II devices as an aid in monitoring the effectiveness of a diabetes control program but not as a tool for diagnosis of—or screening for—diabetes. The FDA clears BGMs and test strips as a complete test system and requires performance testing of the whole system. In evaluating BGM system performance, the factors considered are precision; accuracy in the hands of users; linearity; interferences from common endogenous and exogenous substances; environment (temperature, humidity, altitude); software (conformance to International Electrotechnical Commission Medical Electrical Equipment standards and electromagnetic compatibility); cleaning/disinfection (minimization of contamination with multiuse, estimation of number of cleaning cycles over life of meter, robustness, function of the buttons on the display, cracking, fogging); and labeling (manuals, inserts, quick reference guide, and box and container labels must all be understood by lay users at an eighth-grade reading level).

Ms. Bernhardt summarized her presentation by stating that many factors affect BGM system performance and that each factor is evaluated separately. The user experiences a cumulative effect from all factors, and the FDA strives to make sure that invaluable tools, such as BGMs, can be used safely and confidently for diabetes management.

Session 2: Do Approved Blood Glucose Monitors Perform According to International Organization for Standardization Standards?

Robert Vigersky, M.D., COL MC, Director of the Diabetes Institute at Walter Reed, National Military Medical Center, Bethesda, MD, served as moderator of session 2. Dr. Vigersky introduced the session by sharing that he had visited the website of several online vendors of BGMs, including Walmart, and learned that many BGMs (e.g., Advocate, Clear Choice, Assure, MedSource, Embrace) were available in prices ranging from $5 to $65, strips not included.

He noted that these BGMs had been approved by the FDA but that he could not find data on their performance in a real-world setting. Dr. Vigersky also observed that a wide variety of manufacturers produce these meters, some of them from overseas. After stating that it would be important to all parties to know how well these BGMs perform, Dr. Vigersky introduced the first speaker of session 2.

Do Currently Available Blood Glucose Monitors Meet Regulatory Standards?

Ronald Brazg, M.D., FACE, from Rainier Clinical Research Center, Renton, WA, began by listing the primary uses of SMBG and three factors that interfere with the total accuracy of SMBG, which are patient characteristics/error, interfering substances, and system accuracy. Placing focus on system accuracy, he defined total error (TE) as preanalytical + analytical + postanalytical ***or*** user error + analytical error. Dr. Brazg added that, since 2006, there has been an increasing number of studies comparing BGM performance. Referring to a checklist for accuracy studies,[1] he observed that only 4 out of 20 studies fulfilled at least 8 of 9 criteria and that 50% of those studies fulfilled less than 5 of 9 criteria. Dr. Brazg explained that even with ISO criteria requiring 95% accuracy, a person with diabetes checking BG four times per day could have an unacceptable and clinically significant error every fifth day. Dr. Brazg noted that inherent accuracy and lot-to-lot variability of SMBG systems are often not considered by health care providers in clinical practice. He also observed the growing trend of health care payers basing their SMBG reimbursement decisions solely on cost. As of 2009, one-third of Medicare mail-ordered BGMs come from manufacturers of lower-priced BGM systems. He proceeded to share data from his article[2] that compared seven commercially available systems against the current and proposed ISO criteria. The study showed that only three of seven BGM systems that were tested met the current ISO criteria and only one (ACCU-CHEK) of seven met the proposed ISO accuracy criteria. The results also showed significant lot-to-lot variability among the BGM systems, which illustrated that not all manufacturers have the appropriate quality system that ensures acceptable consistency and performance in the marketplace after approval. In five of seven meters tested, BG results were influenced significantly by hematocrit levels, which can have adverse clinical implications, particularly for patients with chronic kidney disease with anemia by potentially masking hypoglycemia. In conclusion, Dr. Brazg emphasized that the possible impact of inaccurate SMBG systems can put patients at significant risk, resulting in adverse clinical outcomes. Hence, it is important to consider multiple factors, including system accuracy and lot-to-lot variability, in addition to cost, in deciding on insurance formulary coverage, not just cost alone.

Do Approved Blood Glucose Monitors Perform According to International Organization for Standardization Standards? Performance Data for Blood Glucose Monitors, the Ulm View

Guido Freckmann, M.D., from the Institute for Diabetes Technology, Ulm, Germany, began his presentation by defining accuracy as precision + trueness. Precision is based on performance of the strip and BGM, and trueness is the accuracy of the mean. One of the components of DIN ISO 15197:2003 is an evaluation of system accuracy of BGM systems. Dr. Freckmann cited studies that have evaluated system accuracy[1,3] and indicated that more than 40% of BGM systems did not fulfill minimum accuracy requirements. The performance of BGM systems varied from excellent to poor. Other studies also detected lot-to-lot differences.[2,4,5]

Dr. Freckmann recommended that a preapproval evaluation be conducted for precision, system accuracy, and accuracy in the hands of users. After approval, there should be an assessment of each new batch as well as control of BGM systems on the market after approval.

Dr. Freckmann emphasized that accurate BGMs are necessary for making effective clinical decisions. Therefore, quality and system accuracy should be the primary criteria in choosing BGM systems rather than price. Standardized evaluation of BGMs and test strips should be performed to ensure adherence to quality and accuracy standards. These evaluations should be done by an independent party and supervised by government agencies. Legal and funding issues as well as all procedures and reference methods must be clarified and defined. Most importantly, there must be transparency in the results of these evaluations.

Performance of Glucose Meters in Clinical Trials

Andreas Pfützner, M.D., Ph.D., from the Institute for Clinical Research and Development, Mainz, Germany, began his presentation by stating that it is impossible to expect 100% compliance because, in statistics, outliers are necessary. Dr. Pfützner presented data on several studies conducted by the Institute for Clinical Research and Development, one of which was a clinical trial[6] that was performed on various "branded" BGM devices in compliance with the protocol set forth in ISO 15197:2003. The study concluded that the majority of the tested meters are accurate and that these meters would also fulfill the new ISO acceptance criteria. Another study[7] evaluated the accuracy of five BGM systems in a real-world setting, whereas another study[8] studied the importance of proper laboratory training for correct sample handling of glucose oxidase BGMs. Dr. Pfützner concluded with the following points: (1) in the hands of experienced investigators, branded BGMs appear to comply with the new ISO acceptance criteria, while low-cost meters seem to require some improvement in analytical performance; (2) results from "real-world" studies may be an important tool to differentiate standardized ISO testing results from real-life performance; and (3) in light of the multiple factors that interfere with the accuracy and precision of BGMs, complying once with ISO criteria at the beginning of a 3- to 5-year product life cycle of a BGM system appears to be a suboptimal approach to ensuring patient safety and treatment quality.

Performance of Approved Blood Glucose Monitors

Jan Krouwer, Ph.D., from Krouwer Consulting, Sherborn, MA, gave a presentation that focused on bias in clinical trials, sample sizes, and postmarket opportunities. Dr. Krouwer began by noting that ISO 15197 and CLSI POCT12-A3 focus on the error distribution of most samples but that these guidelines do not use error grids. With company studies, bias occurs in many ways: (1) in clinical trials, when a hospital is paid to perform an evaluation, the sponsor specifies the protocol, performs the data analysis, and reviews/edits manuscripts that follow the golden rule "thou shalt not publish bad data." In effect, the evaluation is performed outside of usual laboratory practice and results in an offsite company study rather than a study in the hands of the end user. (2) Clinical trial evaluators often receive more training and could be more highly educated than regular staff, which means that user errors are minimized and actual user error cannot be determined. (3) On the analytical side, lot-to-lot reagent bias is a result of sampling only the lots produced earlier but does not represent reagent lots that are produced later. (4) Bias over time occurs when a first-generation product, which used to equal reference, is replaced by a second-generation product, which now equals reference. However, the first-generation product is no longer equal to the second-generation product and is also not equal to the reference. When the third-generation product is released, the first-generation product and second-generation product no longer equal reference. And so on.

Dr. Krouwer proceeded to show an example from a 2013 proficiency survey by the American Proficiency Institute. The data showed four manufacturers who produced as many as five different versions of BGMs. Dr. Krouwer highlighted the broad range of lowest and highest means as evidence that accuracy could change significantly over time.

With regard to sample size bias, given that there are approximately 8 million Americans with diabetes who take insulin, if they were to test three times per day, it would amount to 7.9 billion glucose tests per year. Therefore, a 100-sample method comparison is a miniscule sample of the population of BGM users. If an adverse event occurred

every 1 million samples, it would be probably not be detected in the 100-sample evaluation but would still occur 7900 times for a particular BGM. Dr. Krouwer explained that, although there is not much that can be done to decrease sample size bias, there is still an opportunity to review these data from the ~8 billion tests to assess BGM postmarket performance using data from proficiency survey results and from complaints and recalls.

In closing, Dr. Krouwer clarified that biases cannot be avoided and that he does not recommend any changes to the FDA approval process. However, Dr. Krouwer believes that postmarket data provides a great opportunity to learn more about BGMs, considering that many factors change over time. Because this is not method comparison data, a series of goals would have to be established for postmarket data to determine what would be considered as acceptable BGM performance.

Premarket and Postmarket Factors That Affect Blood Glucose Meter Performance

Katherine Serrano began her presentation by specifying that BGMs are cleared through 510(k) after demonstrating substantial equivalence to a legally marketed predicate. The FDA does not conduct an independent evaluation of the device and relies on data generated and submitted by the manufacturer. There are limitations to the data received by the FDA and on how the FDA can review the data.

As part of the approval process, manufacturers perform similar sets of studies, but these studies reflect neither actual use nor the actual use environment. For example, most studies are performed in a laboratory and do not account for environmental factors, such as temperature and humidity, and they use newly manufactured components stored and handled by trained personnel in ideal conditions. In addition, study sample sizes are small, and manufacturers do not submit all data from each study.

Ms. Serrano also noted that the current standards for accuracy, which mandate that 95% of test results be within a certain range, still allow 5% (i.e., millions of test strips) to yield erroneous results at any level. She added that small study samples result in large confidence intervals and that these studies do not account for the TE of the system.

Ms. Serrano observed that, although BGMs have become less expensive, smaller, easier to use, faster, and less painful to use over the years, the emphasis of manufacturers has not generally tended to focus on increasing accuracy. She did acknowledge that the revision of the ISO 15197 document seems to have motivated manufacturers to prioritize meter accuracy in recent years.

Ms. Serrano noted that many factors contribute to BGM performance. For example, although the majority of BGMs are designed and validated for over-the-counter (OTC) use only, many OTC devices are used in hospitals and other health care settings (not the intended user). This problem is compounded by that fact that there is currently no distinction between the performance requirements for OTC system use and for professional use. Hence, manufacturers choose the easier route of approving an OTC device and obtaining a Clinical Laboratory Improvement Amendments waiver.

Another factor in BGM performance is the wide range of patients who use BGMs, which results in a high incidence of user error, including but not limited to failing to wash hands before testing, storing test strips improperly, and subjecting the BGMs to temperature and humidity (changes in climate).

Postmarket factors that can affect BGM performance are (1) subpar shipping and temporary storage conditions and (2) manufacturers that do not follow internal specifications during manufacturing and who apply lot release criteria that are too broad. The FDA has to rely on the premarket data being accurate and truthful. Ms. Serrano noted that, while the FDA can conduct inspections on manufacturers once the devices are on the market, such inspections are difficult to conduct, particularly overseas. Ms. Serrano noted that many manufacturers of lesser-known brands also do not provide many medical device reports (MDRs), making it difficult for the FDA to obtain information about postmarket performance of these devices.

Session 3: How Do Approved Blood Glucose Monitors Perform When Used by Patients and Health Care Professionals?

After a lunch break, Courtney Lias, Ph.D., Director, Division of Chemistry and Toxicology Devices, FDA, called session 3 to order and introduced the first speaker.

The Effect of Heat and Humidity on Glucose Strips: Environmental Stress Effects on Point-of-Care Glucose Testing

Richard F. Louie, Ph.D., FACB, assistant professor and center fellow at the School of Medicine at University of California, Davis, CA, provided detailed results of research performed at the Point-of-Care Testing Center for Teaching and Research,[9] with a special focus on the effects of temperature and humidity on BGMs, which can contribute to analytical errors. These effects were studied with simulated disaster and rescue conditions, which were created using an environmental stress-testing chamber.

During Hurricane Katrina, it was reported that new shipments of point-of-care (POC) testing failed after 1 week of use (43.3 °C). Cold temperatures in Springfield, MA, caused glucose meter systems to shut down during emergency response (<12.8 °C). In Haiti, i-STAT whole blood analyzers were rendered inoperable due to high temperatures (35 °C).[10–12]

In modeled simulations, Dr. Louie showed that environmentally stressed glucose-oxidase-based test strips of one glucose meter system generated measurement bias ranging from -65 to 33 mg/dl, whereas glucose-dehydrogenase-based test strips of another meter system generated higher results compared with control after 72 h of exposure in 15 out of 16 cases.[9]

In trials investigating the effect of short-term (shock) thermal (42 °C) and humidity (83%) stress, a maximum bias of 33 mg/dl (29.2%) was observed at 15 and 60 min. In freeze-and-thaw trials, some BGMs operated to some degree after being restored to room temperature, but some meters stayed ineffective. No statistically significant effect was observed in static humidity stress tests, probably because of the moisture barrier achieved with current foil and vial packaging designs, whereas static and dynamic thermal stress caused significant effects.

Dr. Louie summarized the results by stating that (1) static and dynamic thermal stresses can affect the performance of glucose test strips with effects varying between products, (2) the duration of stress appears to affect the performance of glucose test strips, (3) short-term (<1 h) thermal and humidity stresses on the meter can affect glucose measurements, and (4) environmental stress effects on POC glucose monitoring systems appear to be compounded by the effects on meters and test strips, with biases potentially clinically significant.

In addition to taking precautions to store and handle BGM system components properly, Dr. Louie recommended the following: (1) know the effects of environmental stresses on POC reagents and how the stress duration impacts their performance, (2) establish standards for testing and validating the performance of POC reagents and devices using dynamic stresses encountered in field settings, (3) design robust reagents and packaging to protect from adverse conditions, (4) integrate temperature lock-out features on all hospital and consumer POC devices, and (5) plan deployment and resupply schedules for medical supplies, such as reagent test strips, in austere environments to minimize the length of exposure to adverse conditions.

How Do Blood Glucose Monitors Perform in the Intensive Care Unit?

George Cembrowski, M.D., Ph.D., from the University of Alberta Hospital, Edmonton, Canada, started his presentation by stating that, in the intensive care unit (ICU), the "need for speed" has led to widespread use of BGMs. Using 2800 glucose data values collected at their facility from 2004–2012, Dr. Cembrowski demonstrated that their Radiometer arterial blood gas analyzers were as accurate as their core laboratory's analyzer and thus could be used to provide reference glucose values. Next, to assess the accuracy and ease of use of BGMs, Dr. Cembrowski distributed an anonymous survey to 250 nurses using an Internet service, to which 45 nurses responded.

Dr. Cembrowski proceeded to show the results of *x–y* plots of BGM versus reference and *x–y* plots of differences from reference versus hematocrit. The paired data points did not show any obvious trends in two different hematocrit insensitive meters. In a data mining study, Radiometer glucoses and BGM glucose were retrieved and compared if they were run within 60 min of each other for individual patients in the general systems ICU (2500 arterial blood gas, 800 BGM each month). Two distinct models of BGMs were used: one older hematocrit-sensitive model and one newer hematocrit-insensitive model. From the plots of the hematocrit-insensitive BGMs, Dr. Cembrowski observed that outliers had disappeared, there was less glucose variability, hematocrit effect was much smaller, and the magnitude of bias was clinically acceptable.

The nurse survey results showed an increase in product satisfaction with the new BGMs in all usage and testing categories: ergonomics and ease of transport, simplicity of use, ease of placing blood on the strip, ease of cleaning, speed of glucose testing, accuracy, and accuracy for patients with low hematocrit.

In assessing the effectiveness of BGMs in the ICU, Dr. Cembrowski indicated that BGMs are accurate and dependable at their facility for the normoglycemic and hyperglycemic ranges, whereas the lack of data from their general systems ICU prevents him from making a conclusion for the hypoglycemic range.

How Can a Hospital Verify Performance of Blood Glucose Monitors for Severely Ill Patients?

Martha E. Lyon, Ph.D., DABCC, FACB, Department of Pathology and Laboratory Medicine, Royal University Hospital, Saskatoon Health Region, Saskatoon, Saskatchewan, Canada, began by citing three specific issues that need to be addressed in order to establish verification materials and a verification system that will address the unique challenges of critically ill patients: (1) Blood is a complex mixture of cells, water, and dissolved materials, such as glucose. (2) It is assumed that cells, water, and dissolved materials *do not vary* and have *no bias* or influence on glucose results. (3) Critically ill patients can have abnormal amounts of cells, water, and dissolved materials in their blood, related to their severe illness.

Dr. Lyon also explained that, on the analytical side, BGMs measure whole blood specimens, measure glucose activity (i.e., relative molality), and report plasma equivalent glucose concentrations (molarity) achieved with a 1.11 correction factor. However, the formula used assumes that the patient has 43% hematocrit with 93% plasma water concentration and 71% red blood cell water concentration, which does not reflect the blood composition of all patient populations.

Dr. Lyon shared that three variables (hematocrit, plasma water concentration, and red blood cell water concentration) can influence glucose results in critically ill patients and that these errors can be clinically significant. Moreover, these errors are not detected by quality control or external proficiency testing programs.

In closing, Dr. Lyon highlighted the need to establish a verification system with materials that will reflect the distributions of hematocrit and plasma water observed in the critically ill patient population.

Session 4: What Could Be the Consequence of Poor Blood Glucose Monitor Performance?

Dr. Klonoff served as moderator of session 4 and introduced the first speaker.

Adverse Event Reporting System of the Food and Drug Administration

Olga I. Claudio, Ph.D., scientific reviewer at the Division of Chemistry and Toxicology Devices, Office of In Vitro Diagnostic Device and Radiological Health, FDA, began with an overview and a quick explanation of each method used by the FDA to evaluate devices: MDRs submitted by manufacturers, active surveillance by the FDA, trade and consumer complaints received by the FDA, and inspections conducted by the FDA. Recalls are initiated by the manufacturer if a product is defective or potentially harmful. With regard to MDRs and adverse event reports, Dr. Claudio reiterated that, even if any adverse event did not result in an injury, if an adverse event outcome could

have resulted from a patient not receiving help promptly, then the event is considered a serious event and should be reported. It is known that device problems, especially for OTC devices, are usually under-reported. Even so, the FDA receives more than 32,000 BGM MDRs per year. In addition, many factors make it difficult to fully assess the impact of an MDR such as errors or omissions in the MDRs submitted, insufficient description of incidents (missing lot numbers, incomplete device information and patient history), incorrect product codes and categorization of adverse events, and failure to return the device for evaluation. It was also observed that domestic manufacturers appear to be more compliant with reporting requirements than foreign manufacturers.

With regard to inspections, the common observations shared by Dr. Claudio are that some manufacturers do not establish adequate specifications or do not follow their own specifications, do not handle complaints promptly and/or properly, and do not adequately report their data.

In closing, Dr. Claudio shared that the FDA does encounter difficulties in evaluating MDRs because of the volume of data involved and the lack of compliance by manufacturers. However, the FDA strives and continues to work on improving their surveillance of all devices.

Blood Glucose Monitor Surveillance: A European Perspective

Lutz Heinemann, Ph.D., from Science & Co, Düsseldorf, Germany, started his presentation by explaining the complex system that is used to approve medical devices in Europe and obtain the Communauté Européenne (CE) mark. Briefly, the process involves a notified body using evaluators, who are unfamiliar with all new technologies, to assess the safety and performance of a device without evaluating its effectiveness, which would require more clinical data. For example, until 2001, most BGM systems were approved in the Netherlands according to the TNO (Toegepast Natuurwetenschappelijk Onderzoek) quality guideline. However, a study published in 2007 showed that less than 20% of 30 evaluated BGM systems met the tested criteria of the TNOguideline.[13] Other studies showed poor performance by BGM systems as well.[2–4]

This simplistic approach has led to scrutiny and criticism of the CE mark process. One such complaint came from Jackson,[14] who wrote, "need only a simple qualitative certificate (CE mark) to gain access to the market, putting them on the same footing as domestic appliances such as toasters."

How should the authorities react? If 50% of BGMs do not fulfill the new ISO requirements, should they be withdrawn from the market? Manufacturers are quick to dismiss the results of studies that show their devices performing poorly by noting that the studies were most likely funded by a competitor.

This has led Dr. Heinemann to propose establishing the European Institute for Technology Evaluation and Quality Control to conduct independent and objective evaluations of medical devices supervised by the government and funded by manufacturers, insurance companies, and the public. This institute would be able to establish standards and support notified bodies in highly specialized evaluations that are beyond their scope of expertise.

The findings of such an institute will help eliminate the assumption that all BGMs in Europe are the same because they all have the CE mark. The quality of measurement of a BGM can be considered by insurance companies rather than just its price.

In closing, Dr. Heinemann shared that better control and availability of medical devices go hand in hand. There is a need to improve the CE mark approval process to guarantee better medical devices in the European Union, and the changes proposed by the European Union are a step in the right direction. Large, long-term clinical studies need to be performed and registries established to collect data on medical device usage. The European Association for the Study of Diabetes is playing an active role in helping to establish an independent research institution in Europe for medical devices for diabetology. Lastly, Dr. Heinemann invited all parties interested to collaborate and work together to make sure that patients with diabetes have access to effective and safe devices.

The Effect of Poor Blood Glucose Monitor Performance on Calibration of Continuous Glucose Monitors

Howard Zisser, M.D., Director,Clinical Research and Diabetes Technology, Sansum Diabetes Research Institute in Santa Barbara, CA, began the presentation with his conclusions: (1) the more accurate the meter, the better; (2) there are a lot of moving parts, including filtering, smoothing algorithms, and bias, that are operating under the hood; and (3) a "smart" calibration is needed that will help minimize some inherent errors in BGM systems.

Dr. Zisser explained that each component of insulin dosing (i.e., carbohydrate estimation, insulin absorption, insulin sensitivity, and SMBG/continuous glucose monitoring accuracy) is very difficult to measure accurately. In addition, blood glucose levels are constantly changing. Hence, calibration can be likened to attempting to hit a moving target with the added difficulty of using a moving gun. Therefore, Dr. Zisser explained that it is better to focus on the direction, speed, and duration of the glucose movement rather than focusing on one single BG reading. In addition, Dr. Zisser stated that there is no true glucose. It cannot really be measured and does not need to be measured. Glucose *per se* does not matter (except in extreme ranges); only changes in glucose matter.

The main issues are as follows: (1) A technical issue is that tissue samples are used for BG measurements while capillary blood samples are used for calibration. Moreover, tissue estimation is used to predict capillary (or venous) blood values. (2) Blood and tissue have very different dynamics. (3) Blood typically leads the tissue, and tissue levels are reduced compared with the blood level. (4) There is no simple way to measure true tissue glucose.

Other issues that need to be addressed are: (1) when is the best time to calibrate; (2) errors in the calibration device; (3) errors in the tissue measurement; (4) user errors; (5) what is the real goal—estimating true tissue glucose or predicting BG from the tissue reading?

After showing data from two studies on the effect of calibration time on continuous glucose monitoring accuracy and from a modeling experiment that assumed blood and tissue glucose values are correct, Dr. Zisser made the following observations: (1) the time of calibration is very important, (2) meter error is much less important if the calibration time is appropriate, and (3) small errors in the meter can improve BG estimation from tissue measurements but do not improve the ability to estimate true tissue glucose.

In closing, Dr. Zisser mentioned that he would like to propose development of "smart" calibration, which would enable a meter to notify the user when it is time to calibrate.

What Can Simulation Models Tell Us about the Impact of Glucose Meter Error on Insulin Dosing Decisions in the Hospital?

Brad S. Karon, M.D., Ph.D., from the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, MN, began his presentation by explaining that, in preparation to study the impact of BGM bias and precision during tight glycemic control (TGC), the normal distribution of glucose values were first determined by using 6 months of bedside glucose data of patients on TGC from two surgical ICUs (approximately 30,000 BG values, with a median of 116 mg/dl). It was observed that 90% of the values fell into insulin dosing categories that were 20 mg/dl wide, meaning that every 20 mg/dl increment in glucose value led to a change in insulin dose.

The simulation engine randomly sampled values from this data set to produce 10,000 values with the coefficient of variation varying from 0% to +20% and bias varying from -20% to 20%, based upon each initial value sampled. The percentage of simulated values that fell into the same insulin dosing category as the initial values as well as the percentage of 1, ≥2, and ≥3 category dosing errors based on Mayo TGC protocol were calculated. The results were expressed as contour plots that showed the percentage of dosing errors as a function of bias and imprecision. Next, the boundaries for 10%, 15%, and 20% TE were superimposed on the contour plots. The plots showed that allowing 20% TE could result in ≥3 category insulin dosing errors, whereas limiting TE to 15% or 10% would result in no ≥3 category insulin dosing errors. Another simulation was performed using the distribution of glucose values and insulin dosing categories in the Mayo moderate glycemic control (MGC) protocol.

Dr. Karon shared that very similar rates of insulin dosing errors were predicted for TGC and MGC protocols. Only the 20% TE condition allowed large (≥3 category) insulin dosing errors. Unfortunately and notably, many meters perform at this >20% TE.

In an empiric validation of the MGC error model where insulin discrepancy was determined for 4017 paired meter and serum glucose values, the empirically observed dosing errors were close to those predicted by the simulation models.

Rates of severe and moderate hypoglycemia decreased significantly from the time period of TGC to MGC. Given that there was no change in glucose meters, personnel, or the percentage of dosing errors (large insulin dosing errors occurred with both TGC and MGC), this suggests that changing glucose target and insulin dosing categories alone is sufficient to reduce the incidence of hypoglycemia during intensive insulin therapy.

Dr. Karon offered the following conclusions: (1) many glucose meters do not meet ISO 15197 criteria when used in the ICU; (2) 1-category insulin dosing errors are unavoidable; (3) 2-category insulin dosing errors decrease as TE decreases from 20% to 10%; and (4) large dosing errors (≥3 category) occur only at ≥20% TE, but the impact of those errors is a function of the glycemic protocol being used. In protocols with lower glycemic targets, there will be more hypoglycemia, and higher glycemic targets will result in more hyperglycemia. Both cases would have an impact on glycemic variability.

The Incidence of Hypoglycemia Is Related to the Analytical Accuracy of Blood Glucose Monitors: An In Silico *Experiment*

Boris Kovatchev, Ph.D., from the University of Virginia Health System in Charlottesville, VA, introduced his presentation by sharing that most simulations performed to date relate BGM error to insulin dosing error. Given that there is evidence that links BGM error to incidents of severe hypoglycemic episodes in the hospital, using the FDA-accepted University of Virginia/Padova metabolic simulator, Dr. Kovatchev studied the relationship between BGM error and clinical outcome in 100 *in silico* subjects. Experiment 1 studied the rate of detection of hypoglycemia, which was induced by an insulin bolus. Blood glucose measurements were taken at levels between 50 and 70 mg/dl. The four levels of SMBG error studied (5%, 10%, 15%, and 20% random error) yielded mean absolute relative differences of 2.01%, 4.02%, 6.03%, and 8.04%, respectively. Dr. Kovatchev found that the rate of undetected hypoglycemia increased from 0% to 10% as random error increased.[15]

Experiment 2 focused on extreme deviations of blood glucose and ran 45,000 simulation experiments on 100 *in silico* subjects (30 1-day experiments per subject, each repeated 15 times, varying meals and SMBG errors). Three meals were given each day in various times and amounts to simulate real-life conditions. Self-monitoring of blood glucose was used to calculate (1) a premeal insulin amount according to each subject's carb ratio; (2) correction insulin approximately 2 h after each meal according to each subject's individual correction factor to bring BG to 110 mg/dl, with insulin on board taken into account; and (3) hypoglycemia treatment (any time reference BG <70 mg/dl, SMBG was performed, and if SMBG <70 mg/dl, 16 g carbohydrate was given). Five levels of SMBG error were studied (0% equal to reference glucose plus 5%, 10%, 15%, and 20%; random error was defined as bimodal distribution to focus on extreme deviations). The results showed that hypoglycemia increased as BGM error increased. With 8% incidence of hypoglycemia at 0% error, the rate increased to almost 15% probability of hypoglycemia at 20% error rate.

Dr. Kovatchev ended his presentation by reminding the audience how important it is to consider what level of error is acceptable.

How Much Accuracy Is Needed in Blood Glucose Monitors?

Terry Lumber, R.N., C.N.S., M.S.N., C.D.E., B.C.-A.D.M., FAADE, representative of the American Association of Diabetes Educators and Director of the Inova Diabetes Center, Fairfax, VA, began her presentation by stating that she would be sharing insights from the patient's perspective using the AADE7™ self-care behavior categories: healthy coping, medication taking, monitoring, healthy eating, being active, problem solving, and reducing risks. Control of diabetes is

contingent on numerous factors and behaviors. Among the AADE7 self-care behaviors, SMBG is a key component of the treatment regimen.

1. Healthy Coping: Patients may get discouraged when their BGMs are inaccurate. Patients do read or view the product information and want to be assured that their blood glucose results are reliable and accurate. If they discover that their BGM is not reliable and accurate, they are likely to reduce the frequency of their BG checking, which may compromise their glycemic control. Also, educating patients in BGMs and in how to interpret results can result in improved quality of life.

2. Taking Medication: Patients learn how to titrate their insulin doses based on BGM results—using insulin sensitivity factors, insulin correction factors, and carbohydrate-to-insulin ratios. If there are large errors in BG results, then insulin doses would be very inaccurate and possibly dangerous, especially for patients who are highly sensitive to insulin. Patients taking multiple daily injections and insulin and insulin pump users are other groups that require BGMs with high accuracy and precision.

3. Monitoring: Patients need to receive proper training and education on BGM use. Without proper training, patients may not perform self-monitoring and equipment management correctly. Aspects of self-monitoring that can specifically affect accuracy include sample site cleansing (hand hygiene gels may affect BG results, and inadequate cleansing may contribute to contamination of blood sample), obtaining a sufficient blood sample, application of blood sample to the test strip, test strip storage, and meter charging/battery replacement.

4. Healthy Eating: Patients need to know how to respond to variations in carbohydrate intake. Accurate and reliable BG results are important to manage and control glycemic excursions after meals and snacks.

5. Being Active: Patients need to know how to manage BG variations before, during, and after exercise. Accurate and reliable BG results are important to manage glycemic control during exercise.

6. Reducing Risks: Patients are advised to change their brand of meter if their BGM test result averages do not correlate with two separate hemoglobin A1c results. Some educators recommend updating to a new meter every 2–3 years so that patients have access to the most accurate technology for monitoring.

7. Problem Solving: Accurate BGM results are needed to prevent and minimize problems related to hypoglycemia, hyperglycemia, and diabetic ketoacidosis. Especially problematic is undertreating hypoglycemia based on inaccurate BG results.

Ms. Lumber added that there are subpopulations, such as children and infants, who require high accuracy from BGMs because insulin doses are based on weight. Precision is also very important because patients can have multiple meters in use and kept at different places they frequent (e.g., home, office, school, gym, parents' homes). Patients should avoid using different brands of meters concurrently, because error ranges differ.

In closing, Ms. Lumber shared that many diabetes educators or diabetes programs will not recommend or demonstrate a specific brand of BGM to their patients, unless it performs within 15% of a laboratory reference. It is very critical to prevent 2- to 3-category insulin dosing errors to protect the safety of all people with diabetes.

Implications of International Organization for Standardization/Food and Drug Administration Standards and Guidelines on Patient Safety

Dr. Klonoff proceeded to call upon several individuals to provide brief comments on a topic of their choice.

Mr. Larry Ellingson from Global Diabetes Consulting encouraged the FDA to maintain their vigilance in ensuring that manufacturers are in compliance with ISO/FDA standards and guidelines and with their reporting. He also recommended that the FDA, Diabetes Technology Society, and the industry work together to develop guidelines for postmarket surveillance.

Dr. Rolf Hinzmann from Roche expressed concern regarding the market availability of FDA-approved BGMs that perform poorly and also emphasized that system accuracy evaluations for BGMs must be performed in accordance with the respective ISO and CLSI guidelines; if not, their results should not be published.

Mr. Yaron Keidar from Edwards Lifesciences shared that insulin is responsible for more lethal doses than any other drug. Therefore, it is critical to offer better monitoring systems to people with diabetes.

Mr. Christopher Parkin from CG Parkin Communications, Inc., stated that 45% of BGMs have questionable accuracy, which could pose dangerous and deadly consequences. Many manufacturers of these inaccurate meters distribute through mail order and target Medicare with their low prices. In addition to this safety issue, there are also issues with numeracy, illiteracy, lack of face-to-face training and education on BGMs, and what to do with the BG readings.

Dr. David Simmons from Bayer HealthCare expressed concern that the performance data presented to the FDA is not the same as what is delivered in the marketplace. Many manufacturers do not show commitment to quality and do not allocate significant funds and resources to ensure quality control. Unfortunately, there are no enforcement policies in place to ensure that accuracy is maintained by BGMs in the marketplace. This threat to public safety is compounded by insurance payers and the Centers for Medicare and Medicaid Services showing a preference for low-cost BGMs even if they perform poorly.

Jared Watkins from Abbott echoed the concern of many speakers that BGMs are prescribed and reimbursed based solely on their price, which does not take into account the vast amount of effort and resources used by companies to research, develop, and manufacture new devices that comply with increased accuracy standards and to maintain quality control.

Dr. Alan Cariski from LifeScan, Inc., noted that, for patients to have access to a quality product, the financial strain is borne by the manufacturers and the health care system. However, companies cannot compete based on price alone, and this could lead to compromises that can threaten public safety. The FDA has premarket authority but cannot exercise it, because they have to accept at face value the data submitted to them.

At the end of session 4, Dr. Klonoff thanked all speakers and the audience for a successful and informative meeting. With regard to consistent performance of BGMs, Dr. Klonoff concluded that this problem would not be solved even when preanalytical errors are corrected (i.e., physiologic, environmental, interfering substance, and human factor errors). Dr. Klonoff stated that the performance problems highlighted at this meeting go beyond analytical errors and are inherent to the meters. Meter performance at the time of approval is not the same as the data delivered at the marketplace, and this could lead to adverse consequences on health. Modeling shows that these errors result in an increased incidence in 2 and 3 category errors, which is very troublesome and can lead to an increased incidence in hypoglycemia, which leads to metabolic imbalances, demoralization, and poor quality of life. It is clear that additional regulation is needed. Will this need be fulfilled by an independent institute? Surveillance? More studies? Registries? Dr. Klonoff acknowledged that he did not know the answer yet, because the meeting was not about finding a solution, but about identifying a problem. Reiterating the title of the meeting, "Do currently available BGMs meet regulatory standards?," Dr. Klonoff conceded that, unfortunately, all too frequently, the answer is no, they do not.

In closing, Dr. Klonoff affirmed his commitment to ensuring the safety of people with diabetes: "Diabetes Technology Society and I plan to work closely with the regulatory community, the manufacturing community, the academic community, and clinicians to find a solution to the problem identified today. Stay tuned. There is more to come."

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