Better health through laboratory medicine

April 29, 2014
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, Maryland 20862

Dear Sir/Madam:

The American Association for Clinical Chemistry (AACC) welcomes the opportunity to comment on the Food and Drug Administration's (FDA's) January 7, 2014 draft guidance, "*Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use*," which outlines the process manufacturers must employ to acquire blood glucose meter clearance. AACC supports the intent of the document—to improve the quality of these devices and enhance patient care. However, we are concerned that some aspects of the proposed guidance may unnecessarily increase the regulatory burden and costs on the health care system without a corresponding improvement in patient care. We recommend the following changes to the guidance.

Complexity of Device
The FDA suggests that future prescription-use blood glucose monitoring systems (BGMS) submissions "will generally be categorized upon clearance as moderate complexity" (lines 76-78). AACC opposes this change. Although we support the Agency's objective—to distinguish between glucose meters intended for point-of-care use in healthcare settings from those intended for home use—we do not believe that increasing the complexity level of BGMS's will improve patient outcomes. In fact, we are concerned that the opposite may occur if glucose meters are suddenly removed from critical care settings, where they are effectively used to measure and manage glucose levels, thus contributing to better patient outcomes.

In recent years, there have been several reports of patient harm with the use BGMS's in clinical settings. These events were the result of analytical interference issues. We are pleased that the Agency's recommendations outlined in the Interference Evaluation section will address these problems. Reclassifying prescription-use blood glucose monitors as moderately complex will not improve patient safety, but will add to the regulatory burden for health care providers by increasing their personnel documentation, proficiency testing and method performance certification requirements under CLIA'88. AACC believes that greater emphasis is needed on improving the clinical protocols followed by the personnel performing these tests rather than increasing the regulatory requirements associated with using the device.

Precision Evaluation Study
The Agency states that (lines 333-334) "the study should demonstrate acceptable precision for all lots, users and meters." The FDA addresses this question under General Study Design. However, the specifications needed to achieve this objective need to be refined. In order to achieve (line 434) "99% of all values are within ± 10% of the reference method" the %CV of the

meter will need to be < 3.9% IF there is no bias against the reference method AND IF the %CV of the laboratory comparison method is zero. In other words, if the %CV of the meter is > 3.9% it will be impossible to achieve the accuracy criteria specified under General Study Design. Further, 3.9% may only be a starting point for glucose meter precision; 2.5% or even 2.0% may be the goal. The actual performance of the "comparison method" and subsequent uncertainty in the glucose value need to be considered when setting accuracy requirements for the BGMS device as described in the study design.

General Study Design

The Agency states (lines 281-283) that "the term "reference method" refers to a laboratory based glucose measurement method that has been well-validated for precision and accuracy, and that is traceable to a higher order, e.g., internationally recognized, reference material and/or method." The only current reference methods for glucose are: the Centers for Disease Control and Prevention (CDC) hexokinase method and several isotope dilution mass spectrometry (IDMS) methods. Methods such as blood gas analyzer electrodes, Yellow Springs Instruments (YSI) or other routine main laboratory methods, may be traceable to reference methods but are not reference methods.

The Agency should consider using a different term in lieu of "reference methods," such as "comparison method," "predicate method" or "laboratory method traceable to a reference method." In addition, the performance requirements for the "comparison method" need to be defined (e.g., imprecision <3% CV at glucose concentrations of 80-300 mg/dL).

The BGMS guidance also states (lines 390-392) that "Testing should be performed by the intended POC (point of care) user (e.g., nurses, nurse assistants, etc.) to accurately reflect device performance in POC settings" for method comparison studies, since this will encompass potential user error. AACC agrees that performance of glucose meters should be evaluated with nursing and end-users as operators; however the guidance does not indicate who should perform testing in the laboratory. AACC recommends that the document clarify that clinical laboratory personnel should perform the laboratory comparison method. Also, a time constraint for performing the "reference method" should be given as glucose will decrease 7% per hour in whole blood.

The FDA states (lines 398-400) that a manufacturer making claims for using the meter in populations that are vulnerable to potential interferences "should include patients in surgical and medical intensive care units." AACC agrees that method comparison studies should be designed to include these patients. In addition to medical and surgical intensive care units (ICU) patients, the agency should include Cardiac, Pediatric, Neurology, Trauma, Burn ICU patients (if such patients are to be tested) as well since these patients can have very different metabolic disturbances (electrolyte, water balance) and exposure to different drugs and other therapies.

The FDA states (lines 432-438) that *"In order to demonstrate that a BGMS device is sufficiently accurate to be used safely by health care professionals, you should demonstrate that 99% of all values are within ± 10% of the reference method for glucose concentrations ≥ 70 mg/dL, and within ± 7 mg/dL at glucose concentrations < 70 mg/dL. To avoid critical patient management errors, no individual result should exceed ± 20% of the reference method for samples > 70 mg/dL or ± 15mg/dL < 70 mg/dL."*

AACC agrees with improving the accuracy of hospital meters above that of ISO 15197. We are concerned, however, that the FDA is raising the bar too high and could stifle clearance of meters that are improvements over current devices but unable to reach this level of accuracy. Several peer-reviewed modeling studies suggest that BGMS meters can be used successfully and safely for glycemic control when they achieve a total error between 10-15%.[1] The consensus of CLSI POCT12-A3 was to use the midpoint of this target for total error, and therefore the acceptable performance goal for meters used in hospitals is ± 12.5% (±12 mg/dL at <100 mg/dL). This accuracy goal for validating a meter in a hospital setting is more than adequate and ought to be achievable by BGMS; consequently we recommend that FDA modify the specification to ± 12.5%.

We are also concerned with the requirement (lines 436-438) that 100% of meter values should be within "± 20% of the reference method." Such a finding is virtually impossible to prove statistically, requiring tens of thousands of samples to "prove" that 100% of meter values are within 20% of the "reference method." The Agency should modify the guidance document to reflect the accuracy criteria (as modified) discussed in the previous paragraph.

The FDA states (lines 451-453) that "We expect that to meet the clinical needs of the user population, BGMS devices intended for prescription-use should minimally be able to measure blood glucose accurately down to 10 mg/dL and up to 500 mg/dL." It is not clear that the ability to quantify concentrations between 10 and 20 mg/dL would lead to any change in the management of patients. AACC believes the lower limit of quantification of 10 mg/dL is unwarranted; 20 mg/dL is adequate.

[1] Karon BS, Boyd JC, Klee GG. Glucose meter performance criteria for tight glycemic control estimated by simulation modeling. Clin Chem. 2010;56 (7):1091-1097; Boyd JC, Bruns DE. Monte Carlo simulation in establishing analytical quality requirements for clinical laboratory tests: meeting clinical needs. Methods Enzymol. 2009;467:411-33; Breton MD, Kovatchev BP. Impact of blood glucose self-monitoring errors on glucose variability, risk for hypoglycemia, and average glucose control in type 1 diabetes: an in silico study. J Diabetes Sci Technol. 2010; 4(3):562-70.

Interference Evaluation
The FDA requests evaluation to "reference method" (implying a laboratory-based glucose method), yet in the summary table examples within the guideline (Tables 5 and 6, pages 18 & 22), the YSI is listed as the "mean glucose value" for comparison. Does this occurrence mean that the YSI is the preferred reference method? AACC recommends that the guidance document take a more general approach by providing performance requirements that outline what constitutes an acceptable "reference" method.

The FDA guidance document states (lines 557-559) that "you should evaluate the effect of potentially interfering endogenous and exogenous substances and conditions on device performance, such as icterus, lipemia, and varying hematocrit levels, as well as the effect of common medications." AACC suggests that the Agency modify this sentence and reference CLSI EP7, which is routinely used by manufacturers for almost all interference studies and is an FDA-recognized standard. This revision will simplify the document and covers all interference studies including drugs, endogenous substances, hematocrit and oxygen.

The FDA lists the potential interferents for BGMS devices (Table 4, pages 16-17). AACC suggests the FDA add dobutamine to this list. It is a much more commonly used pressor than dopamine in critical care areas. We also question why testing is being done at normal "therapeutic" concentrations of endogenous substances such as creatinine, cholesterol, bilirubin, hemoglobin (soluble or total?), uric acid? If there is no interference at the high concentrations it is typically unnecessary to test the lower concentrations.

The document states (lines 716-718) that "You should also evaluate the effect of oxygen on the performance of the device to assess whether it can safely be used across the claimed blood oxygen range in the intended use population." This evaluation should only apply to glucose oxidase methods.

Test Strip Lot Release Criteria
The guidance doesn't specifically provide test strip lot criteria, but states (lines 1024-1026) that "if the device has an average CV of 3% and an average bias of 5% these may be considered." If a device has a bias of 5% and a CV of 3% it will be impossible for 99% of the meter values for that lot to fall within 10% of the reference value, so these two performance goals in the document are incompatible with each other. We suggest the Agency use the same accuracy criteria used in the method comparison section against a laboratory method but with a smaller sample size and internal personnel performing the testing rather than end users.

For Precision using Whole Blood Samples
The Agency states (lines 1035-1040) that "This study should be completed over 10 days using whole blood samples spanning the BGMS device's stated measuring range. Spiking samples with glucose, or including samples in which glucose was allowed to glycolyze is acceptable in

order to evaluate the extreme end of the system's measuring range. At least two BGMS devices should be included in this study and at least 10 measurements should be taken per glucose level, per meter." This provision should be less prescriptive, requiring instead that the manufacturer have a validated method for lot release.

As currently recommended, the Agency proposal will require manufactures to complete the study over 10 days, necessitating that they perform a significant number of lot release tests on numerous lots on any given day. This proposal will place a tremendous burden on manufacturers, including the storage of large numbers of strip lots at the facility, the need for extensive staffing to perform the studies and the maintenance an adequate supply of whole blood to complete the required testing. AACC believes these requirements are unreasonable.

We are not aware of any evidence that the current lot release process validated by every manufacturer is inadequate. There is also no evidence that the proposed method would improve the detection of poorly performing lots. Therefore, the magnitude of the testing proposed by the guidance is unduly burdensome. Currently used and statistically justified sample size and test duration will continue to be adequate to detect any of the failures this approach is designed to address.

Labeling

The manufacturer labeling is recommended (lines 1118-1119) to "include limitations against … tight glycemic control use." As current CLSI guidelines for meter accuracy were based upon the best available evidence linking meter accuracy to patient outcomes during glycemic control, we believe this limitation is unnecessary and will only cause confusion on the part of hospitals and laboratories using BGMS devices for this purpose. Labeling is also (lines 1120-1122) supposed to limit the use of meters to calibrate continuous glucose monitoring systems or entering results into insulin dosage calculators for dosage recommendations. Many BGMS devices currently recommend calibration against a capillary fingerstick sample measured on a glucose meter. Therefore, the FDA needs to answer the following questions in the guidance:

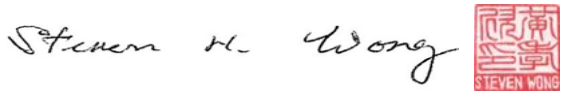
- Will current BGMS devices need to revalidate their calibration labeling and verify specific manufacturers that can be used for calibration?

- What are the specific protocols that should be used for BGMS manufacturers to prove that their devices can be used for BGMS calibration, or more commonly in hospital use, that glucose meter results can be entered into insulin dose calculators?

- If this limitation stands, will it require laboratories to validate their electronic medical record system calculations and/or commercial systems offering insulin dose calculations for use with specific meter manufacturers and device models?

By way of background, AACC is the principal association of professional laboratorians--including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and practice in hospitals, independent laboratories and the diagnostics industry worldwide. The AACC provides international leadership in advancing the practice and profession of clinical laboratory science and medicine and its applications to health care. If you have any questions, please call me at (336) 716-2639, or Vince Stine, PhD, Director, Government Affairs, at (202) 835-8721.

Sincerely,



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