



# Performance of Blood Glucose Meters in the Low-Glucose Range: Current Evaluations Indicate That It Is Not Sufficient From a Clinical Point of View

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System accuracy requirements for blood glucose (BG) meters (BGMs) are defined in standards (1) or guidance documents (2). In 2013, International Organization for Standardization (ISO) 15197:2013 stated that BGMs are acceptably accurate if  $\geq 95\%$  of their measurement results are found within  $\pm 15$  mg/dL (0.83 mmol/L) or  $\pm 15\%$  (whichever is larger) of reference results (1). The 2014 U.S. Food and Drug Administration (FDA) draft guidance for over-the-counter BGMs requires  $\geq 95\%$  of results within  $\pm 15\%$  and  $\geq 99\%$  of results within  $\pm 20\%$  across the whole glycemic range (2). Thus, if a patient's BG true concentration is 60 mg/dL (3.33 mmol/L), acceptably accurate results range from 45 to 75 mg/dL (2.50 to 4.16 mmol/L) according to the ISO limits and from 51 to 69 mg/dL (2.83 to 3.83 mmol/L) according to the FDA criteria. Two questions arise:

1. Do current BGMs fulfill these criteria?
2. If a BGM cannot reliably differentiate between 50, 60, and 70 mg/dL (2.77, 3.33, and 3.88 mmol/L), how useful are predefined hypoglycemia thresholds?

From a safety point of view, these questions are relevant when patients measure their BG concentration (e.g., in case of hypoglycemia symptoms).

Furthermore, these questions are important when BGMs are used in clinical trials (e.g., for documentation of the occurrence of hypoglycemic events). Recent evaluations of current BGMs showed considerable differences in performance in the low-glucose range (3,4). This might be one reason why the FDA does not accept BG measurement data from point-of-care or self-monitoring BGMs as evidence for the efficacy of any insulins or antidiabetes drugs with regard to reduction in hypoglycemic events. Consequently, this raises the question of which BGMs can be used in clinical trials that aim at showing a benefit in terms of hypoglycemia risk that must document a sufficient accuracy in the low range.

This issue is complicated by system accuracy requirements being applied to measurement results from the whole glycemic range. If a BGM shows 100% accurate results at BG concentrations  $\geq 80$  mg/dL (4.44 mmol/L) (80% of results, following ISO 15197:2013), this results in 25% of the samples in the low-glucose range being allowed outside the accuracy limits (5% "results outside of accuracy limits" divided by 20% "results  $< 80$  mg/dL [4.44 mmol/L]").

Recent publications suggest that it is possible to achieve a large number of results in the low glycemic range by

carefully adjusting subjects' BG concentrations in vivo (3,4). If in vivo adjustment does not yield enough low-BG results, a possible alternative is offered in form of the glucose clamp technique. This technique keeps BG concentrations at a defined level for some time, including at low concentrations (5). In systematic studies that allow for multiple participations of the same subject, the glucose clamp technique provides a methodological advantage. In either case, subject safety should be a major concern regarding the possible negative effects of recurring or prolonged hypoglycemia.

We wonder whether, from a clinical point of view, greater interest should be displayed in the performance of BGMs in the low glycemic range. This could also help in the documentation of benefits of novel drugs with respect to reduction in hypoglycemia risk.

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clinical trials. S.P. is an employee of Institut für Diabetes-Technologie Forschungs-und Entwicklungsgesellschaft (IDT) (Ulm, Germany), which carries out studies on the evaluation of BGMs and medical devices for diabetes therapy on behalf of various companies. G.F. is general manager of IDT. G.F. and IDT have received speakers' honoraria or consulting fees from Abbott, Bayer, Berlin-Chemie, Becton Dickinson, Dexcom, Menarini Diagnostics, Novo Nordisk, Roche Diagnostics, Sanofi, and Ypsomed. No other potential conflicts of interest relevant to this article were reported.

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G.F. take responsibility for the content of the article.

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