Clin Chem Lab Med 2010;48(7):1021–1027 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2010.226

SKML-Quality Mark for point-of-care test (POCT) glucose meters and glucose meters for home-use

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Abstract

Background: Point-of-care glucose meters are used increasingly in semi- and non-professional context. The quality of glucose measurements depends on the quality of the equipment, the quality of use, and the pre-analytical conditions. In this article, a External Quality Assessment Scheme (SKML)-Quality Mark for point-of-care test (POCT) and self-test glucose meters is proposed, assessing analytical quality and technical quality. The analytical requirements are based on the biological variation concept, and a system to assess meters for the SKML-Quality Mark is described. Using the proposed system as an example, 14 meters were tested.

Methods: The analytical quality of the POCT and self-test equipment was assessed for *plasma calibrated* glucose values by comparison with a trueness verified method traceable to the IFCC reference method in an accredited clinical laboratory. The concept is based on the biological variation system. The SKML-Quality Mark comprises the following criteria for blood glucose equipment: 1) Fulfilment of compliance with ISO 15197 and/or TNO guideline criterion; 2) Fulfilment of the total allowable error (TAE) criterion; 3) Fulfilment of the total allowable linearity bias criterion; 4) Fulfilment of the total allowable interfering substances bias criterion; and 5) Fulfilment of the haematocrit criterion.

Results: The proposed SKML-Quality Mark system was tested on 14 commercial home-use meters. The TAE criterion is violated by two meters. The main reason for the violation is bias. For the majority of meters, the Passing and Bablok regression confidence interval does not include the intercept of 0.0 and slope of 1.0. In addition, Syx indicates dispersion around the line or non-linearity. The bias and total error at three different concentrations were investigated as part of the quality mark, resulting in disapproval of the Dicomed Sensocard Plus meter. The bias was significant for the Wellion Linus. With respect to interfering substances, bias of the same magnitude and sign as the bias without additive was seen for all meters for acetaminophen, indicating no additional interference. For ascorbic acid, an additional bias was seen for several meters. However, significant bias was demonstrated for the Sensocard Plus and Glucocard X-meter.

Conclusions: The biological variation concept offers a scientific basis for assessment of acceptable deviation. The concept is extended in the SKML-Quality Mark correcting for the limited number of measurements that can be performed while assessing home-use or POCT meters. The results show that three out of 14 meters fail the proposed quality mark.
Clin Chem Lab Med 2010;48:1021–7.

Keywords: bias; biological variation; point-of-care test (POCT); quality; total error.

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Received October 25, 2009; accepted February 17, 2010; previously published online May 12, 2010

Introduction

This study deals with the everlasting dilemma between analytical quality specifications applied by regulatory bodies and professional medical communities. Failure of the European In-Vitro Diagnostic (IVD) medical devices directive (1) to define specifications critical for the clinical usefulness of point-of-care test (POCT) systems paved the way for this dilemma. For several POCT assays, e.g., INR (International Normalised Ratio) and glucose, the combination of analytical quality and pre-analytical conditions yields a total variation budget which often far exceeds the medical professional requirements for safe diagnosis and monitoring, even though specifications by ISO and the CE marking are not exceeded. Outsourcing POCT systems to general practitioners (GPs) or patients performing their own measurements is widespread and adds significantly to the total variation due to variability in the end-user's skills and insights in the use and interpretation of POCT assays.

Recently in the Netherlands, the Health Care Inspection stated (2) that the measurement of glucose and glucose POCT equipment in health care institutes should be under the responsibility of the clinical laboratory, and thus under the responsibility of the clinical biochemist. Measurements should be performed in a controlled setting with a central role for the clinical laboratory. In addition, users of POCT equipment should be trained by the laboratory. This is in line with the requirements of the final draft of the ISO 22870 international standard (3).

The IVD directive (1) includes essential requirements for self-tests. It was implemented in The Netherlands with the Decree on In-Vitro Medical Devices. The 2007 Annual Report on Population Screening of the Health Council of The Netherlands (4) focuses on the value of self-testing and investigates the quality. The IVD essential requirements refer to analytical quality as well as diagnostic utility and clinical usefulness. In the ISO 15197 (5) and 22870 standards, requirements for self-testing and POCT equipment are described, as are in the TNO Quality Guideline Blood Glucose Monitors (6). The analytical quality of self-test and POCT equip-

ment has been studied extensively (7–10). For medical tests in general, there is consensus about the analytical requirements in relation to diagnostic utility and clinical usefulness. These requirements are based on the biological variation concept as described by Fraser (11, 12). Data on biological variation and analytical requirements derived from this were compiled by Ricos et al. (13) and Westgard (14) in a database for a large number of clinical laboratory tests. However, neither the IVD directive or the ISO or TNO guidelines mention these requirements.

In this article, a (External Quality Assessment Scheme) SKML-Quality Mark for POCT and self-test glucose meters is proposed, assessing analytical quality and technical quality. The analytical requirements are based on the biological variation concept, and a system to assess meters for the SKML-Quality Mark is described. Using the proposed system as an example, 14 meters were tested.

Materials and methods

The quality of a glucose measurement using a POCT or self-test meter depends on the quality of the equipment, the quality of how it is used, and the pre-analytical conditions. The SKML-Quality Mark assesses the quality of the equipment on two aspects: analytical quality based on the biological variation concept, and technical quality based on the ISO 15197 and the TNO guideline.

Analytical quality

To assess the analytical quality of the equipment in relation to the diagnostic utility and clinical usefulness, the analytical goal is based on the biological variation concept. The analytical quality of the POCT and self-test equipment is assessed using *plasma calibrated* glucose values compared with a trueness verified method traceable to the IFCC reference method in an accredited clinical laboratory. In this investigation, the hexokinase method using the Roche Integra (Nederland BV, Almere, The Netherlands) with plasma obtained from centrifuged heparinized whole blood was used. To correct for any bias in the hexokinase method on a specific day of testing, commutable and IFCC reference method targeted SKML Calibration 2000 samples (15, 16) were also measured. During the study period, no bias from the reference materials was observed.

The analytical quality of 14 different types of meters was tested type by type. Five meters of each type were evaluated.

To assess the quality of one type of glucose POCT or home-use meter, three 6 mL heparinized venous blood samples (without separator gel) were obtained from an apparently healthy person, who was not taking any medication. An aliquot of 0.5 mL was removed through the cap of a tube, centrifuged and analysed for glucose using the comparison method. Using a needle, an aliquot (1 μL for 6 and of 2 μL for 10 mmol/L) of a 45% glucose solution in water was added through the caps of two of the tubes to produce glucose concentrations of approximately 6 mmol/L and 10 mmol/L, respectively. The third tube was maintained until the glucose concentration was about 3 mmol/L. Aliquots of 0.5 mL were removed though the caps of the three tubes, centrifuged and analysed for glucose using the comparison method 10 times each. Immediately following the completion of centrifugation, measurements using the comparison method and the glucose meters were started. The measurements were performed within 120 s for the 25 measurements at each concentration, and within 240 s for the 50 measurements for estimation of imprecision. In addition, pO_2 was measured in the three tubes for meters using the glucose oxidase method. For glucose meters using this method, the partial pressure of oxygen in the sample is required that is comparable to the pO_2 in capillary blood. Therefore, tubes were mixed prior to the procedures until the pO_2 was within 8.0 and 12.0 kPa. Whole blood glucose measurements were performed by sampling blood through the caps of the tubes and applied to the five meters we investigated that used this method in each session.

The imprecision of the handheld equipment was estimated at a glucose concentration of 6 mmol/L using 50 measurements, 10 on each of the five meters that were tested per type of meter (total 50 measurements per type of meter) using two different lots of test strips. The bias of the handheld equipment was estimated from 75 measurements, five measurements at each of three concentrations, on each of the five meters. Total error was also estimated from the basis of the combined 75 measurements.

Linearity was assessed using three concentrations of 3, 6 and 10 mmol/L, according to the Passing and Bablok regression.

Interference from acetaminophen was assessed by splitting freshly drawn heparinized venous blood into two 1 mL aliquots, adding 1 μL of a concentrated solution (66 mmol/L) of the substance to a final concentration of 66 μmol/L, and the same amount of saline (154 mmol/L) to the second aliquot. Glucose was measured in each of the aliquots using five meters. From each of the aliquots, 0.5 mL was centrifuged and plasma glucose was measured five times using the trueness-verified Roche Integra hexokinase method.

Interference from ascorbic acid was assessed in essentially the same way (using a concentrated solution of 170 mmol/L ascorbic acid) at a final concentration of 170 μmol/L.

The effect of haematocrit was assessed by measuring the haematocrit in three heparinized venous blood samples having glucose concentrations of approximately 3, 6 and 10 mmol/L. Each sample was centrifuged, and for each glucose concentration, four portions were prepared with haematocrit values of approximately 0.25, 0.35, 0.45 and 0.55. The haematocrit was measured using a Sysmex 2500 analyzer (Sysmex Nederland BV, Etten-Leur, The Netherlands). Glucose in each portion (with the pO_2 between 8.0 and 12.0 kPa) was measured in duplicate on two meters and in the plasma obtained after centrifugation using the hexokinase method.

Statistical methods

We used the known within- and between-person variation. For glucose, the within-person variation, CVw, is 5.7% and the between-person variation, CVb, is 6.9%. From these the allowable bias (AB) is calculated as

$$AB = 0.25 \times \sqrt{(CVw^2 + CVb^2)} = 2.23\%.$$

The desirable analytical variation

$$CVd = 0.5 \times CVw = 2.9\%$$

and the total allowable error (TAE)

$$TAE = AB + (1.65 \times CVd) = 7.0\%.$$

However, with these calculations a definitive known target value is assumed. In the present study, there is an uncertainty component in the estimation of the target value. This uncertainty is accounted for under the next section ‘uncertainty in target value of the trueness verified method’.

Uncertainty in target value of the trueness verified method The target values μ and standard deviation (SD) σ of the trueness verified method are estimated from a limited set of measurements, introducing additional uncertainty depending on the number of measurements. The target value is estimated from 10 measurements at each of three levels. The imprecision of the hexokinase method was CVt = 1.6%. The confidence interval (CI) for μ (P 95%) is

$$X-1.96\times CVt/\sqrt{30}\le\mu\le X+1.96\times CVt/\sqrt{30}$$

or

$$X-0.57\%\le\mu\le X+0.57\%.$$

At each individual level the uncertainty is (P 99%):

$$X-2.58\times CVt/\sqrt{10}\le\mu\le X+2.58\times CVt/\sqrt{10}$$

or

$$X-1.31\%\le\mu\le X+1.31\%.$$

Uncertainty of bias The bias of the POCT meters was estimated on the basis of 15 measurements on each of five meters, i.e., 75 measurements. The CI (P 95%) of the true mean μ_m at a CVd of 2.9% is

$$Y-1.96\times CVd/\sqrt{75}\le\mu_m\le Y+1.96CVd/\sqrt{75}$$

where Y is the mean of the 75 measurements. Then

$$Y-0.65\%\le\mu_m\le Y+0.65\%.$$

Thus, on the basis of 75 measurements and including an uncertainty in the target value of 0.57%, the AB

$$AB_{max}=AB+conf(ref)+conf(Y)=2.23\%+0.57\%+0.65\%=3.5\%$$

(first column of Table 2A and B).

At each individual level (25 measurements, P 99%)

$$AB_{max}=2.23\%+2.58\times CVt/\sqrt{10}+2.58\times CVd/\sqrt{25}$$
$$=2.23\%+1.31\%+1.50\%=5.0\%$$

(right part of Table 2A describing the AB at a low, middle and high concentration of glucose determined with 25 measurements at each level).

Uncertainty of imprecision The imprecision σm of the meter was estimated from 50 measurements, 10 in each of five meters at a concentration of 6 mmol/L. The CI (P 95%) of σm is

$$\sqrt{(n-1)CVd^2/a}\le\sigma m\le\sqrt{(n-1)CVd^2/b}$$

where a = 31.6 and b = 70.2 from the χ^2-table at 49 degrees of freedom. Then, for CVd = 2.9%, the CI for σm is 2.4% ≤ σm ≤ 3.6%. Thus, on the basis of 50 measurements, the upper limit for the imprecision was CVd_{max} = 3.6% (Table 2A).

A second measure of imprecision is the residual SD of regression, Syx, calculated in the linear regression (see Linearity).

Uncertainty in total error The total error was estimated from 75 measurements. The CIs of bias and imprecision resulted in a TAE (P 95%) of:

$$TAE=AB_{max}+(1.65\times CVd_{max})=3.45\%+1.65\times 3.6\%=9.4\%$$

(left side of Table 2A).

At each individual level and using the Syx from the linear regression as estimate for imprecision TAE (P 99%) was

$$TAE=5.0\%+2.33\times 3.6\%=13.4\%$$

(right side of Table 2A).

Linearity Linearity of the blood glucose meters was assessed using three sets of five samples each at glucose concentrations of 3, 6 and 10 mmol/L. Samples were analysed on five meters, and in replicates of five with the hexokinase method. Using the method of Passing and Bablok, the line Y = a + bX was calculated, including the CIs (P 95%) for the intercept and slope. If the confidence limits of intercept and slope did not include 0.0 and 1.0, respectively, the bias at individual levels was inspected.

A measure of imprecision is the residual variance Syx. A large Syx indicates large dispersion around the line, or non-linearity. Since linearity was estimated from measurements at three concentrations, the CI of Syx was estimated at P 99%. The CI for Syx was

$$\sqrt{(n-1)CVd^2/a}\le Syx\le\sqrt{(n-1)CVd^2/b}$$

where a = 47.9 and b = 104.0 from the χ^2-table at n − 2 = 73 degrees of freedom. Then, for CVd = 2.9%, the CI for Syx is 2.4% ≤ Syx ≤ 3.6%. This allowable Syx (ASyx) of 3.6% was used (Table 2A). Syx was used in the estimation of TAE at individual concentrations. The total error at individual concentrations was estimated from the bias at that concentration and the CV as estimated from the 50 measurements.

If intercept or slope exceeded the limit, the bias at each individual concentration was compared with AB_{max} at that concentration, and if these exceed the total error at each concentration they were compared with the TAE at that concentration level.

Interfering substances The interference from different substances was tested at therapeutic levels (for each substance five measurements at five meters). Acetaminophen and ascorbic acid were tested at final concentrations of 66 μmol/L (10 mg/L) and 170 μmol/L (30 mg/L), respectively. The maximum AB (P 99%) AB_{max} was

$$AB_{max}=AB+2.58\times CVt/\sqrt{5}+2.58\times CVd/\sqrt{5}$$
$$=2.23\%+1.85\%+3.35\%=7.4\%$$

(Table 2B).

At a CVd_{max} of 3.6%, the TAE for interfering substances (P 99%) was

$$TAE=AB_{max}+2.33\times CVd_{max}=5.9\%+2.33\times 3.6=14.3\%$$

(Table 2B).

Technical quality

Prior to measurements, handheld blood glucose meters should, at a minimum, comply with the ISO 15197 standard and/or the TNO guideline. These documents include, in addition to aspects of safety,

analytical requirements. The most important aspect in the TNO guideline is that it allows a 15% deviation in glucose values obtained with a handheld meter vs. the hexokinase method, and ISO 15197 allows for a 20% deviation vs. the reference method (type to be chosen by the manufacturer).

SKML-Quality Mark

The SKML-Quality Mark comprises the following criteria for blood glucose equipment:

1. Fulfilment of compliance with ISO 15197 and/or TNO guideline criterion.
2. Fulfilment of the TAE criterion.
3. Fulfilment of the total allowable linearity bias criterion.
4. Fulfilment of the total allowable interfering substances bias criterion.
5. Fulfilment of the haematocrit criterion.

If a meter failed one of the criteria, the data were inspected for possible outliers that influenced the results using Box and Whisker plots. If an outlier was detected, it was removed and the results recalculated.

A SKML-Quality Mark approved meter should be used by appropriately trained personnel or patients.

Comparison of user-meters with the laboratory

The quality of the analysis should be checked regularly using control materials for POCT equipment, and at least once a year for home-use meters by comparison of a measurement by the user with the laboratory method. Assessment of a measurement on a home-use blood glucose meter was done as follows. The patient performed a measurement in the same manner he/she normally performs measurements, in duplicate. At the same time, heparin blood was collected from the patient for plasma glucose. The plasma glucose was also measured in duplicate.

Results

The proposed SKML-Quality Mark system was tested as an example on 14 commercial home-use meters (Table 1). The blood glucose meters were tested according to the procedure described in Methods. The first SKML benchmark criterion is in compliance with ISO 15197 or the TNO guideline. All 14 meters fulfilled this criterion. All calculated SKML-Quality Mark parameters are shown in Table 2A and B. For example, the results for the Abbot freedom lite meter (second row in Table 2A and B) included a bias of –4.2% (mean value of 75 measurements of 7.493 mmol/L vs. a hexokinase mean of 7.733 mmol/L); CV of 2.9% resulting from 10 measurements on each of five meters using the same sample with a concentration of approximately 6 mmol/L; bias and CV combine for a TE of 4.2 + 1.65 (2.9) = 8.9%; bias at a concentration of 5 mmol/L was –7.1% (mean value of 25 measurements of 4.720 mmol/L vs. a hexokinase mean of 5.080 mmol/L; bias of –5.3% at a concentration of 6.5 mmol/L (mean of 6.196 vs. 6.540); bias of –0.1% at a concentration of 11.5 mmol/L (mean of 11.564 vs. 11.580); TE of –11.9 at a concentration of 5 mmol/L resulting from a bias of –7.1% and 1.65 times the CV of 2.9%; TE of –10.0% at 6.5 mmol/L resulting from the bias of –5.3% and the CV of 2.9%; TE of –4.9% at 11.5 mmol/L resulting from a bias of –0.1% and a CV of 2.9%; Table 2B: bias of –4.2% if no additive [equal to first bias column in Table 2A; acetaminophen concentration of 10 mg/L, bias of –1.3% (mean of one measurement in each of five meters of 5.980 vs. hexokinase mean of 6.060); ascorbic acid concentration of 30 mg/L, bias of –2.8% (mean of 4.240 vs. hexokinase mean of 4.460)]. Table 2A shows that the total error for the Wellion Linus was 16.2%, and for Glucocard X-meter was 13.4%, both larger that the TAE of 9.4%. Total error at individual levels (Table 2A) were –30.2% for Wellion Linus and –18.1% for Glucocard X-meter at the low level. Total error as 13.9% for Sensocard plus at the middle level and –13.6% for Glucocard X-meter at the high level. The presence of acetaminophen resulted in bias of –12.9% for Wellion Linus (Table 2B). The presence of ascorbic acid resulted in a bias of 11.9% for Sensocard plus and 8.7% for the Glucocard X-meter. Table 3 summarizes the five SKML benchmark criteria for the 14 meters. Figure 1 shows the results of the second benchmark criterion.

Discussion

The quality of analytical processes has been a major topic in laboratory medicine for many years. Internal and external quality assessment makes good sense. The introduction of total quality systems and accreditation has enhanced the quality of medical laboratories, including the pre- and post-analytical aspects. Since the introduction of POCTs, the necessity for quality assessment of such measurements has become increasingly clear (17). International and national guidelines and regulations put the responsibility for the performance of the POCT in the hands of the medical labora-

Table 1 Blood glucose meters, company, type and test principle, tested for the SKML-Quality mark.

Company	Type	Test principle
Abbott	Freestyle freedom	Dehydrogenase
Abbott	Freestyle freedom lite	Dehydrogenase
Abbott	Freestyle lite	Dehydrogenase
Abbott	Freestyle mini	Dehydrogenase
Abbott	Precision X-ceed	Dehydrogenase
Bayer	Contour	Oxidase
Boeren	Wellion Linus	Oxidase
Dicomed	Sensocard plus	Oxidase
Lifescan	One touch ultra 2	Oxidase
Lifescan	One touch ultra easy	Oxidase
Lifescan	One touch vita	Oxidase
Menarini	Glucocard X-meter	Dehydrogenase
Roche	Accuchek aviva	Dehydrogenase
Roche	Accuchek compact plus	Dehydrogenase

Abbott BV, Amersfoort, The Netherlands; Bayer BV, Mijdrecht, The Netherlands; Boeren Medical BV, Tilburg, The Netherlands; Dicomed BV, Zwolle, The Netherlands; Lifescan Benelux, Tilburg, The Netherlands; A. Menarini Diagnostics Benelux NV, Valkenswaard, The Netherlands; Roche Diagnostics Nederland BV, Almere, The Netherlands.

Table 2A Proposed SKML-Quality Mark results for 14 POCT/home-use meters (part 1).

SKML-QM			AB_{max}%	CVd_{max}%	TAE%			ASyx%	AB_{max}%			TAE%	
			3.5	3.6	9.4			3.6	Bias%			TE%	
Company	Type		Bias%	CV%	TE%	Y = a + bx	Conf (a)	Conf (b)	Low	Middle	High	Low	Middle	High
Abbott	Freestyle freedom	A	0.0	3.1	5.1	Y = –0.12 + 1.04X	–0.47 to 0.15	0.95–1.12	–1.5	6.5	–4.9	–6.7	11.6	–10.0
Abbott	Freestyle freedom lite	B	–4.2	2.9	8.9	Y = –0.97 + 1.10X	–1.55 to –0.68	1.05–1.18	–7.1	–5.3	–0.1	–11.9	–10.0	–4.9
Abbott	Freestyle lite	C	–1.4	*4.7*	9.1	Y = –0.84 + 1.09X	–1.35 to –0.42	1.03–1.18	–3.2	0.7	–1.7	–11.0	8.5	–9.4
Abbott	Freestyle mini	D	3.4	2.2	7.1	Y = –0.19 + 1.06X	–0.28 to –0.02	1.04–1.09	2.5	4.6	2.3	6.1	8.3	6.0
Abbott	Precision X-ceed	E	–0.5	4.9	8.6	Y = –0.50 + 1.10X	–0.80 to –0.28	1.05–1.16	–5.3	4.7	–1.0	–13.4	12.8	–9.1
Bayer	Contour	F	–0.2	3.2	5.4	Y = 0.06 + 0.98X	–0.00 to 0.20	0.96–1.00	1.6	0.3	–2.4	6.9	5.6	–7.7
Boeren	Wellion Linus	G	–10.3	3.6	**16.2**	Y = –1.72 + 1.17X	–2.03 to –1.60	1.14–1.22	–24.3	–5.8	–0.7	**–30.2**	–11.7	–6.6
Dicomed	Sensocard plus	H	0.9	3.8	7.2	Y = –0.38 + 1.09X	–0.88 to 0.16	0.99–1.21	1.4	7.6	–6.3	7.7	**13.9**	–12.5
Lifescan	One touch ultra 2	I	0.6	2.3	4.4	Y = –0.53 + 1.10X	–1.13 to –0.19	1.06–1.17	4.1	–6.4	4.0	7.9	–10.2	7.8
Lifescan	One touch ultra easy	J	–4.8	2.1	8.2	Y = 0.07 + 0.93X	–0.14 to 0.14	0.92–0.96	–2.9	–4.9	–6.4	–6.4	–8.4	–9.9
Lifescan	One touch vita	K	–3.2	3.6	9.1	Y = 0.09 + 0.95X	0.03 to 0.28	0.93–0.96	–1.4	–2.4	–5.7	–7.3	–8.3	–11.7
Menarini	Glucocard X-meter	L	–9.2	2.6	**13.4**	Y = –0.50 + 1.00X	–0.88 to –0.23	0.95–1.08	–13.8	–4.4	–9.3	**–18.1**	–8.7	**–13.6**
Roche	Accuchek aviva	M	1.6	1.9	4.8	Y = –0.11 + 1.03X	–0.31 to 0.04	1.02–1.06	5.1	–2.2	2.0	8.2	–5.3	5.2
Roche	Accuchek compact plus	N	–0.1	1.8	3.0	Y = –0.00 + 1.00X	–0.10 to 0.15	0.98–1.02	2.8	–2.6	0.1	5.7	–5.6	3.1
Roche	Integra	O	0.0	1.6	2.6									

CV% in italics: one outlier removed. Bold printed: violation of TAE criterion.

tory. The market for POCT and self-test equipment is large, and the number of tests and equipment that appear on the market is increasing markedly. It is the responsibility of the profession of clinical chemistry and laboratory medicine to assess the quality of these tests (18). The SKML-Quality Mark for POCT and self-test blood glucose meters presented in this paper should facilitate this.

SKML-Quality Mark

The SKML-Quality Mark is based on the analytical requirements for measurement as defined by the biological variation concept. The rationale of this concept is that in clinical diagnosis and monitoring, analytical random variation must be kept so low that numerical changes in test results in an individual do reflect changes in that person, and not analytical noise. The concept is widely accepted in the field of clinical chemistry and laboratory medicine. The Quality Mark is used to test meters. However, an approved meter does not guarantee a good measurement. Inappropriate use, deterioration, incorrect preservation of strips and other preanalytical errors may lead to incorrect measurements (19). A serious example is given below. Therefore, regular supervision by an accredited medical laboratory is essential to guarantee adequate results.

The selected meters were the most frequently used meters by patients in the diabetes policlinic of the hospital of one of the authors.

In the present ISO 15197 standard, a deviation of 20% from the target value is accepted. However, the 20% deviation was based on what was technically possible at the time the ISO standard was agreed upon. Previous studies (9) have suggested that a TAE of 15% presents a risk for diabetics to incorrectly dose insulin. Whatever TAE criterion is suggested by medical professionals in this study or other studies, it is always much more restricted than the ISO specifications referred to by manufacturers and sets the stage for everyday analytical quality of glucose POCT systems in the marketplace. The struggle for improvement carries on, supported by this study that provides a clinically relevant model for benchmarking of glucose POCT systems. The biological variation concept offers a sound scientific basis for assessment of medically acceptable deviation. The concept is extended in the SKML-Quality Mark correcting for the limited number of measurements that can be done while assessing home-use or POCT meters. The results show that three out of 14 meters fail the proposed quality mark.

Results for 14 meters (Table 3)

The TAE criterion was violated by two meters (Wellion Linus and Glucocard X-meters). The main reason for the violation is bias. For the majority of meters, Passing and Bablok regression CI does not include the intercept of 0.0 and slope of 1.0. The bias and total error at three different levels was inspected as part of the quality mark. This resulted in disapproval of the Wellion Linus, Dicomed Sensocard Plus, and Glucocard X-meters. A significant bias was observed in the presence of acetaminophen for Wellion

Table 2B Proposed SKML-Quality Mark results for 14 POCT/home-use meters (part 2).

SKML-QM		No additive	Acetaminophen 66 μmol/L	Ascorbic acid 170 μmol/L
		AB_{max} 3.5%	AB_{max} 7.4%	AB_{max} 7.4%
Company	Type	Bias%	Bias%	Bias%
Abbott	Freestyle freedom	0.0	–3.6	–6.8
Abbott	Freestyle freedom lite	–4.2	–1.3	–2.8
Abbott	Freestyle lite	–1.4	–1.7	6.4
Abbott	Freestyle mini	3.4	–1.3	–5.7
Abbott	Precision X-ceed	–0.5	–2.8	5.7
Bayer	Contour	–0.2	–5.9	–4.1
Boeren	Wellion Linus	–10.3	**–12.9**	6.4
Dicomed	Sensocard plus	0.9	3.6	**11.9**
Lifescan	One touch ultra 2	0.6	–2.6	–6.4
Lifescan	One touch ultra easy	–4.8	–2.0	–6.0
Lifescan	One touch vita	–3.2	–0.3	NM
Menarini	Glucocard X-meter	–9.2	0.8	**8.7**
Roche	Accuchek aviva	1.6	–5.1	3.2
Roche	Accuchek compact plus	–0.1	–6.7	4.1

Bold printed: violation of interfering substances bias criterion.

Linus. Ascorbic acid caused an additional bias for the Sensocard Plus and Glucocard X-meters.

All measurements were performed in samples having haematocrits within the specifications of the manufacturer. The measurements at four haematocrit levels revealed no additional deviation (data not shown).

SKML-Quality Mark in practice

Meters that complied with the SKML-Quality Mark were recommended to nurse practitioners and patients. Approved meters were the Abbot freestyle freedom, freestyle freedom lite, freestyle lite, freestyle mini and precision X-ceed; Bayer Contour; Lifescan one touch ultra, one touch ultra easy and one touch vita; Roche Accuchek aviva, Accuchek compact plus. Disapproved meters were Boeren Wellion Linus; Dicomed Sensocard plus; Menarini glucocard X-meter. An approved meter does not guarantee good measurement. Users were trained to perform measurements and their performance was assessed on a regular basis. To show that such a system is essential and therefore part of the SKML-Quality Mark, we briefly discuss an example for measurements performed by one patient. This patient used an approved meter. At his biannual assessment, the patient measured a glucose value of 10 mmol/L using his own meter. The result from the laboratory for a plasma sample was 5 mmol/L. The patient was asked to send in his meter. Assessment revealed that the meter showed a structural positive bias of 50%, caused by an unknown factor. The patient was on insulin and frequently had hypoglycaemia because of overdosing insulin. Thus, for

Table 3 Results for 14 POCT/home-use meters as tested with the proposed SKML-Quality Mark benchmark criteria.

SKML-QM			ISO 15197 or TNO	TAE%	TAE% linearity	AB interference	Haematocrit
Company	Type			9.4%	13.4%	7.4%	0.25–0.55
Abbott	Freestyle freedom	A	OK	OK	OK	OK	OK
Abbott	Freestyle freedom lite	B	OK	OK	OK	OK	OK
Abbott	Freestyle lite	C	OK	OK	OK	OK	OK
Abbott	Freestyle mini	D	OK	OK	OK	OK	OK
Abbott	Precision X-ceed	E	OK	OK	OK	OK	OK
Bayer	Contour	F	OK	OK	OK	OK	OK
Boeren	Wellion Linus	G	OK	**Failed**	**Failed**	**Failed**	OK
Dicomed	Sensocard plus	H	OK	OK	**Failed**	**Failed**	OK
Lifescan	One touch ultra 2	I	OK	OK	OK	OK	OK
Lifescan	One touch ultra easy	J	OK	OK	OK	OK	OK
Lifescan	One touch vita	K	OK	OK	OK	OK	OK
Menarini	Glucocard X-meter	L	OK	**Failed**	**Failed**	**Failed**	OK
Roche	Accuchek aviva	M	OK	OK	OK	OK	OK
Roche	Accuchek compact plus	N	OK	OK	5.7	OK	OK

Bold printed: violation of criterion.

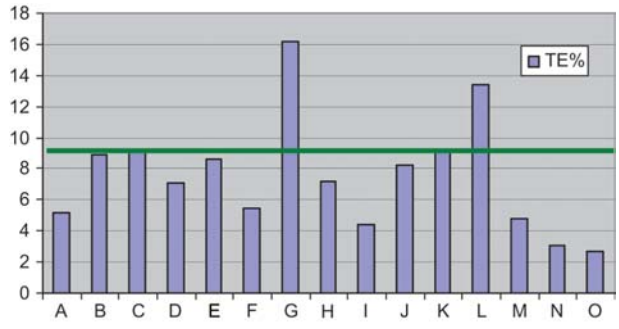

Figure 1 Total error of the 14 meters in relation to the total allowable error (thick horizonatal line).
Letters correspond to Table 2A. For comparison, the result of the comparison method (Roche Integra plasma hexokinase) is depicted as O.

evaluation of measurements by patients, it is necessary to assess the combination of the patient's handling on their own meter (which should be an approved meter), the patient's strips and the patient's blood. The expertise of an accredited laboratory is essential for such evaluation.

Conclusions

The SKML-Quality Mark is based on the analytical requirements for measurement as defined by the biological variation concept. The quality mark was tested using glucose meters and revealed that most of the 14 meters tested complied with the requirements. However, three meters failed. It is the intention to introduce the Quality Mark in The Netherlands as advice for glucose meters in use for POCT and at home. The Quality Mark will be issued at three locations in The Netherlands by ISO 1589 accredited medical laboratories. Other laboratories will be encouraged to set up systems for assessment and control of the performance of end-users of approved meters.

Acknowledgements

The authors wish to thank Mrs. Rianne van de Ven-de Win for skilful performing the analyses.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

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