

# Problems and Practical Solutions in the External Quality Control of Point of Care Devices with Respect to the Measurement of Blood Glucose

William Graham Wood

## Abstract

Point of care testing (POCT) is evolving at an ever increasing rate. This article deals mainly with the aspect of POCT for blood glucose and the problems of external quality assessment (EQA) of point of care devices (POCD). At the present time it is only possible to control precision with EQA, independent of the matrix of the test materials (synthetic polymer-base, plasma/serum, or processed whole blood). The German Federal Medical Council guidelines for laboratory performance allow an interlaboratory imprecision of  $\pm 16\%$ . The majority of POCD fulfill these requirements. The long-term stability of results—tested by repeated distribution of the same materials over a 12-month period—is excellent, and the performance of POCD under routine conditions is usually excellent in terms of result-comparability. The problems of accuracy in terms of control materials have still to be mastered.

*J Diabetes Sci Technol 2007;1(2):158-163*

## Introduction

Point of care testing (POCT) is in itself nothing new; simple tests for blood glucose and ketones have been available in tablet and test-strip form for half a century.<sup>1-4</sup> The novelty of POCT is the increasing complexity of the analytical devices and their compactness due to the development in microelectronics. An example is in the development of the Gemsaec centrifugal analyzer (Electro-Nucleonics International Ltd., Breda, Netherlands) of the 1970s<sup>5,6</sup> to the Piccolo POCT analyzer (Abaxis Inc., Union City, CA) of the 1990s,<sup>7,8</sup> with the former being a stand-alone analyzer interfaced to an external computer and the latter being a self-contained portable device

weighing less than 7 kg and taking up half a square foot of space.

The introduction of these more complex point of care devices (POCD) into decentralized units, such as doctors' offices, coupled with their black-box nature (it is often not possible for the user to influence performance by adjustment of hardware or software), makes it imperative that they are subject to independent control. This is best performed using external quality assessment (EQA), with the aim being the reduction of incorrect results to a minimum.

**Author Affiliation:** Institute for the Promotion of Quality Assessment in the Medical Laboratory (INSTAND e.V.), Duesseldorf, Germany

**Abbreviations:** (cv) coefficient of variation, (EQA) external quality assessment, (EQAS) external quality assessment scheme, (GC) gas chromatography, (INSTAND) Gesellschaft zur Förderung der Qualitätssicherung in medizinischen Laboratorien e.V., (IDMS) isotope-dilution mass spectrometry, (POCT) point of care testing, (POCD) point of care device, (RiliBÄK) Richtlinie der Bundesärztekammer, (RMV) reference method value

**Keywords:** accuracy, blood glucose, diabetes mellitus, evaluation, external quality assessment, external quality assessment schemes, home testing, point of care devices, point of care testing, precision, quality control

**Corresponding Author:** Prof. William G. Wood, INSTAND e. V., Ueberstrasse 20, D-40223 Duesseldorf, Germany; email address [wood@instand-ev.de](mailto:wood@instand-ev.de)

INSTAND (Gesellschaft zur Förderung der Qualitätssicherung in medizinischen Laboratorien [= society for the promotion of quality control in medical laboratories]) has been running EQA surveys for POCD for several years, with these being mainly, but not exclusively, concerned with the measurement of blood glucose and qualitative urinalysis (stix).<sup>9</sup> Additional programs for lactate and clinical chemistry analytes, for example, for the different rotors for the Abaxis®-Piccolo, have been introduced into the EQA schemes offered by INSTAND. The trend toward decentralized laboratory analyses will continue at an increasing rate due to the development in miniaturization and cost effectiveness of patient-near testing when coupled with rapid decision making. It is therefore logical to optimize both internal and external control of the performance of POCD.

Point of care testing is usually performed on fresh whole blood samples, whereas external quality control requires at least transport of samples to the participant. The problems associated with EQA of POCT begin at this point. These problems have been tackled by INSTAND over the past decade, which have resulted in compromises between theory and practice.

### The INSTAND Experience: Practical External Quality Assessment with Flaws

The rest of this article deals mainly with problems and possible solutions in POCT concerned with the monitoring of blood glucose. General problems relevant to other areas of POCT are discussed briefly, especially where theory and practice are still widely separated.

Articles have already been published from this laboratory<sup>10,11</sup> that deal with the problems of internal and external quality control of POCD, which are cited here, so that those interested can study the full details. Selected points are dealt with later.

The original aim in the EQA of blood glucose POCD was to conceive a single sample suitable for all devices. This has not been achieved up until the present time, so that three different matrices have to be used for each survey, namely processed whole blood, plasma/serum,

and synthetic polymer-based samples, each spiked with known amounts of glucose.<sup>11</sup>

The EQA schemes concentrate on controlling precision rather than accuracy, with the latter only being indirectly controllable.

The guidelines of the Federal Medical Council (Richtlinie der Bundesärztekammer, RiliBÄK) from 2001<sup>12</sup> require that a reference method is used for setting target values for accuracy for the EQA of plasma glucose. The reference method uses gas chromatography (GC) combined with isotope-dilution mass spectrometry (IDMS).<sup>13</sup> Because calibration of the POCD sensors using amperometric detection is lot specific, a reference method cannot be used to set target values for such devices. This results in the use of device-specific consensus values as target concentrations, for both internal (with lot-specific codes or "calibration sensors") or external (device-specific concentrations) quality control. Some producers claim to have improved the quality of production of the sensors, with regard to measured concentration, so that lot-specific calibration (=adjustment) is no longer necessary. Similar considerations must be taken into consideration with test strips using chemical reactions, where the new lot code must be entered into the device when changing lots. As can be seen, the precision can be checked directly, the accuracy only indirectly (in terms of the precision of internal control materials compared with the concentration ranges allowed for the given lot number).

This situation makes it difficult for a meaningful statistical analysis of results for small groups ( $n \leq 6$ ). Because some suppliers produce several devices for different sectors of the market, which give different values using processed materials, this "splitting effect" is enhanced, as shown in **Table 1**, which summarizes results from a quality control survey run in January 2006. The right-hand column in **Table 1** (ratio sample 11:sample 12) has been included to show that the calibration of devices is not the same. Even if the devices measure the EQA samples "constantly wrong," the ratio between the measured concentrations should remain constant. As can be seen, this is not the case, even when statistically nonvalidated results ( $n \leq 6$ ) are excluded.

**Table 1. Results from EQAS January 2006, Samples 11 and 12: Processed Whole Blood<sup>a</sup>**

Device (no. of participants) <sup>b</sup>	Sample 11 (median) (mg/dl)	Sample 12 (median) (mg/dl)	Sample 11 / Sample 12
AccucheK–Sensor (n = 173)	56.0	131	0.427
AccucheK–Plus <sup>c</sup> (6)	93.0	186	0.500
Accutrend (32)	58.0	133	0.436
Glucometer / Ascensia-Elite (53)	40.0	116	0.345
Glucometer / Ascensia-Dex (1)	50.0	147	0.340
Ascensia Contour (18)	45.5	113	0.403
GlucO Men (8)	46.0	134	0.343
Medisense (28)	87.0	148	0.588
Care Diagnostics (12)	69.5	130	0.535
Omnitest-Sensor (3)	39.0	128	0.305
One-Touch–Profile (1)	69.0	138	0.500
One-Touch–One Touch II (3)	64.9	124	0.523
One-Touch–Basic (3)	65.0	125	0.520
One-Touch–Ultra <sup>d</sup> (31)	39.6	130	0.305
Glucotronic (1)	45.0	122	0.369
Reflux (1)	73.0	114	0.641
RLT-Super-GL (21)	62.0	127	0.488
GlucO Touch (1)	66.0	127	0.520
HemoCue–Sample set 2 <sup>e</sup> (118)	320	130	
RMV–GC-IDMS (1)	65.1	132	0.493

<sup>a</sup> Reference method values (RMV)–GC-IDMS: sample 11, 65.1 mg/dl; sample 12, 132 mg/dl; ratio sample 11:sample 12 = 0.493. Allowed concentration range according to RiliBÄK and RMV: sample 11, 54.7–75.5 mg/dl [3.03–4.19 mmol/liter]; sample 12, 110–153 mg/dl [6.10–8.50 mmol/liter].

<sup>b</sup> Devices with  $n \leq 6$  cannot be evaluated statistically. These are listed for information. The distribution of devices used reflects the situation on the German market with regard to hospital and doctors' offices. It may not reflect the home-use situation.

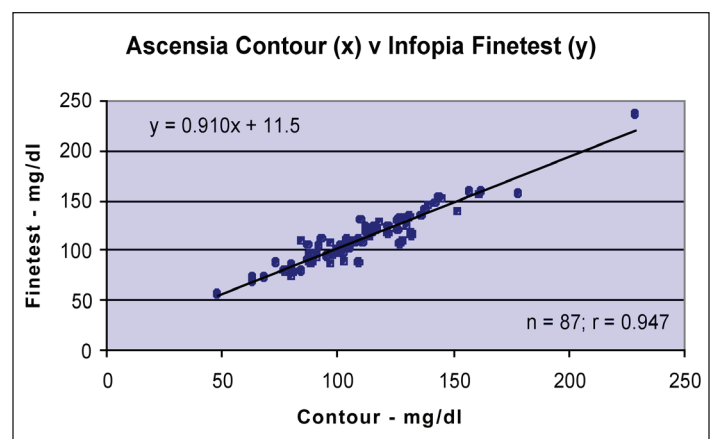
<sup>c</sup> The AccucheK plus uses test strips.

<sup>d</sup> The One-Touch Ultra uses sensors with amperometric detection, whereas other One-Touch devices use test strips with reflectometric detection.

<sup>e</sup> The samples here cannot be compared directly as they were plasma based, whereas the rest of the samples used processed whole blood.

Even using processed whole blood, which is the most similar material to that used “at source,” results from the EQA survey cannot be compared for accuracy. The variations in concentrations measured as expressed by the mean and standard deviation are  $59.4 \pm 15.8$  mg/dl for sample 11 and  $132 \pm 16.5$  mg/dl for sample 12, resulting in coefficients of variation of 26.6 and 12.5%, respectively. Such results, when observed superficially, may lead to the conclusion that POC devices are not acceptable with regard to accuracy when compared with a reference

method procedure. If we look at the daily practice, things begin to look different. **Figure 1** shows a comparison made with a member of staff who was given two POC devices, one from a market leader and the other from a far-eastern producer, with the request to test both devices under routine conditions once a day over a 3-month period. The Ascensia Contour<sup>®</sup> (Bayer Vital GmbH, Leverkusen, Germany) device is calibrated to measure whole blood glucose at the time of this comparative study electrochemically using glucose dehydrogenase. (Since September 2006, a new Ascensia Contour<sup>®</sup> POCD has been calibrated to measure plasma glucose and has a new coenzyme that makes the method specific for glucose<sup>14</sup>). The Finetest<sup>™</sup> (Infopia Co. Ltd., Anyang, Korea) device uses glucose oxidase, potassium ferricyanide, and a carbon electrode for the amperometric measurement and is calibrated to give plasma glucose values using whole blood as a sample. The results show quite clearly that the performance of both systems is numerically similar (median: Ascensia Contour<sup>®</sup> 106 mg/dl; Finetest<sup>™</sup> 109 mg/dl), the correlation between both systems is excellent (unpaired  $t$  test:  $p = 0.715$ ), and that one system does not constantly read higher/lower than the other (paired  $t$  test:  $p = 0.119$ ).



**Figure 1.** Comparison between Ascensia Contour<sup>®</sup> and Finetest<sup>™</sup> point of care devices used under routine conditions for self-monitoring of blood glucose.

As stated earlier, the choice of materials for EQA of POC devices depends more on the nature of the device (measuring principle) than on the nature of the sample<sup>10,11</sup> and the fact that whether one uses a synthetic matrix, processed plasma, or processed whole blood only results in a shift in problems rather than their solution! A few selected examples are given in the following paragraphs.

Some POCD perform in EQA surveys with a given matrix, but not with another. An example is the test-strip devices from Johnson & Johnson—the Lifescan One-Touch<sup>®</sup> and

GlucoTouch® series (LifeScan Inc. Milpitas, CA) (with the exception of the One-Touch Ultra®, which operates with sensors). These operate best using processed whole blood controls, with other materials (plasma, serum, polymer-based controls) often giving different error messages. INSTAND EQA surveys use different dyes for coding the polymer (polyethylene glycol-20000)-based controls. These are either red with similar absorption maxima to hemoglobin (e.g., nuclear fast red or alizarin red) or intensive blue (e.g., copper phthalocyanine, crystal violet, or methylene blue) with the aim of “tricking” the devices to accept the controls as blood samples. The One-Touch and Gluco-Touch devices use a chemical reaction with a chromophore, which is intensively blue, with the blue color being directly proportional to the glucose concentration in the sample. Whereas red dyes had no effect on the concentration read, blue dyes, especially methylene blue, gave a positive bias of up to 30% (see **Table 2**). Because the use of serum or plasma with these devices has often led to error flags, only processed whole blood is used in EQA surveys (INSTAND Survey #805).

**Table 2. Effect of Different Dyes on Results from Three Point of Care Devices for Blood Glucose<sup>a</sup>**

Dyestuff	One-Touch Basic (mg/dl)	Gluco Touch	AccucheK Sensor (mg/dl)
Alizarin red	93	Error 2	159
Bordeaux red	95	Error 2/248 mg/dl	160
Nuclear fast red	96	Error 1	157
Crystal violet	107	Error 2	161
Cu phthalocyanine	111	Error 2	158
Methylene blue	125	Error 2	160

<sup>a</sup> Weighed-in glucose concentration: 150 mg/dl [8.32 mmol/liter]. The One-Touch Basic and Gluco Touch devices are from Johnson & Johnson (Lifescan); the AccucheK Sensor is from Roche Diagnostics. Values from blue dyes were significantly higher than from red dyes ( $p < 0.05$ ). The Gluco Touch device gave error readings in 35/36 determinations (six for each dyestuff), with the only numerical concentration being with bordeaux red as the dye.

Polyethylene glycol-based control materials worked well for all sensor-operated devices, with good interlaboratory precision being obtained in all cases. The Ascensia Elite® POCD using glucose oxidase gave significantly higher results than the Ascensia Contour® POCD, which uses glucose dehydrogenase as an indicator enzyme when using polymer-based samples. The results here for two samples from 2005 (reference method value [RMV] for sample 11/05, 74.6 mg/dl; for sample 12/05, 155 mg/dl) were Ascensia Contour® ( $n = 24$ ), sample 11/05:  $43.2 \pm 1.97$  mg/dl [cv 4.56%]; sample 12/05:  $79.0 \pm 6.77$  mg/dl [cv 8.56%]—no outliers, Ascensia Elite® ( $n = 75$ ), sample 11/05:  $49.4 \pm 5.89$  mg/dl [cv 11.9%]; sample 12/05:

$139 \pm 9.39$  mg/dl [cv 6.76%]—two outliers for sample 11/05, three outliers for sample 12/05.

Comparative results for the same devices using plasma samples with similar concentrations (samples 51/05 and 52/05—RMV 54.0 and 158 mg/dl, respectively) were Ascensia Contour® ( $n = 17$ ) sample 51/05:  $48.8 \pm 4.76$  mg/dl [cv 9.75%]; sample 52/05:  $170 \pm 10.0$  mg/dl [cv 5.88%]—no outliers, Ascensia Elite® ( $n = 28$ ), sample 51/05:  $42.8 \pm 5.35$  mg/dl [cv 10.8%]; sample 12/05:  $157 \pm 7.19$  mg/dl [cv 5.17%]—no outliers. The concentrations measured in plasma were reversed, inasmuch as those from the Ascensia Contour® were higher than those from the Ascensia Elite®.

Results for the processed whole blood samples in **Table 1** for these devices were Ascensia Contour® ( $n = 18$ ), sample 11/06:  $46.7 \pm 3.46$  mg/dl [cv 7.41%]; sample 12/06:  $115 \pm 7.39$  mg/dl [cv 6.43%]—no outliers, Ascensia Elite® ( $n = 53$ ), sample 11/06:  $39.7 \pm 4.76$  mg/dl [cv 12.0%]; sample 12/06:  $116 \pm 6.51$  mg/dl [cv 5.61%]—one outlier for sample 11/06, two outliers for sample 12/06. (Numerical differences are due to the fact that here the mean and, in **Table 1**, the median concentrations were used.) At lower concentrations (sample 11/06) the Ascensia Elite® gave lower values, whereas at higher concentrations (sample 12/06) both devices gave the same results.

The overall imprecision, as expressed by the coefficient of variation, was similar, regardless of sample matrix, whereas the accuracy, compared with the reference method value, varied according to the sample matrix. Although the examples were taken from Bayer Devices, they can be used to exemplify matrix-dependent differences also found with other producers’ devices.

## Other Evaluation Methods and Results for Point of Care Devices

Results published that “evaluate” the performance of POC devices often compare the performance of the latter with a laboratory routine method. Such comparisons lead to a “worst-case scenario” inasmuch as the results are only indirectly comparable due to the following points.

1. There is a time lag between sampling with the POCD and that of measurement on the clinical chemistry analyzer (even though this may only be a few minutes).
2. The device is tested with samples from different sources (arterial, venous, mixed blood) from different patients with different hemoglobin oxygen tension (possibly affecting results in sensor systems using glucose oxidase as an electron generator) and different anticoagulants (EDTA, heparin).

This does not mean that such comparisons are useless, but they must be seen in context. Results from the field test shown in **Figure 1** are optimal because they only have one variable, namely the POC device used for measurement. The difference in the slope of the regression line in **Figure 1** between Ascensia Contour<sup>®</sup> and Finetest<sup>™</sup> devices most probably results from the calibration (whole blood versus plasma plus different enzymes for detection). Satisfactory results were found when comparing the Ascensia Contour device with a routine method using a Norwegian national scheme evaluation protocol (Skandinavisk utprøving af laboratorieudstyr til Primærsektoren).<sup>15</sup> In this study, the goals of the International Standards Organization 15197<sup>16</sup> and American Diabetic Association were met initially.

## POCT–Quo Vadis?

In the past decade the trend toward minimizing the time between the clinical decision to perform an analysis and the implementation of therapy on receipt of results has accelerated so that POCT is playing an even more important role in laboratory life. With the continual development in electronics and computerization, together with the vast commercial market for such devices, POCT is already an active “competitor” in the field of classical clinical chemistry.

Today POCT is already established in many areas of medical care. The determination of blood glucose is performed in the emergency unit, intensive care unit, rehabilitation, general outpatient care, neonatology, and by self-monitoring at home. Blood gas analysis has moved from the laboratory to the intensive care unit, the operating theater, and emergency unit. Thrombelastography has become an integral part of prehospital care in emergencies, as well as in cardiac and thoracic surgery units.<sup>17,18</sup> Clinical chemistry panels are used in emergency admission, in military field hospitals, and in neonatal units. Cardiac markers are used in the preclinical phase (ambulance), emergency admission, and cardiac outpatient clinics, and drug monitoring is used in forensic areas, neonatal care, and rehabilitation and for compliance in geriatric care.<sup>19</sup> The reliability of POCD has improved, so that in many cases, the quality of results can be directly compared with on-site clinical chemistry analyzers.<sup>15</sup>

## Conclusions

With the increasing use of POCD in the decentralized control of diabetics, it is imperative that such devices are controlled independently by means of EQA schemes. This must be limited at the present time to hospitals and doctors’ offices. The control of self-monitoring of blood

glucose at home lies in the responsibility of the patient and indirectly with the doctor responsible for treatment, which in turn lays the emphasis on continuing patient education.

The problems of monitoring accuracy by means of EQA surveys have not been fully resolved, with the accent being on the control of precision at the present time. Whereas the use of POCD for monitoring of blood glucose can be advocated, they are still not recommended for the initial diagnosis of diabetes mellitus.

The observations made in the POCT of blood glucose and diabetes can be extended to other fields as far as external quality assessment is concerned, especially with regard to sample composition and the control of precision rather than accuracy.

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