System Performance Summary

SURE SMART Blood Glucose Monitoring System

ISO 15197:2013 / EN ISO 15197:2015 REQUIREMENTS

Date: October 2018

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1. Objective

Self-monitoring of blood glucose is associated with improved outcomes in people with diabetes.[1-5] Particularly for patients on insulin therapy, self-monitoring of blood glucose may lead to better glycemic control.[5,6]

Our goal is to demonstrate that the 4SURE Smart blood glucose monitoring system (BGMS) performance is in compliance with the requirements set forth by ISO 15197:2013 / EN ISO 15197:2015[7] and therefore reliable. A third party was asked to assess system accuracy and measurement precision.

2. 4SURE Blood Glucose Self-Monitoring System

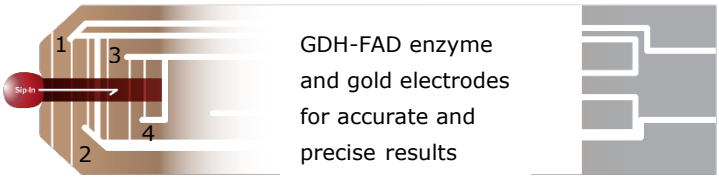
4SURE Smart is a blood glucose monitoring device (*in vitro* diagnostic use). It can be used at home for self-testing or at a clinic by a healthcare professional to assist in the management of type 1, type 2, and gestational diabetes.

Table 1: 4SURE Smart system specifications

Blood sample	Capillary blood samples from the fingertip or alternate sites; healthcare professionals may also use arterial, venous, and neonatal heel blood samples.
Sample size	0.5 µL (glucose)
Reaction time	5 seconds (glucose)
Reagent enzyme	GDH-FAD
Measurement range	0.5~33.3 mmol/L
Operating range	Hematocrit (HCT) range: 0~70% Temperature: 8 ~ 45°C
Calibration	No coding
Detection	• Audible fill detection • Plasma value detection • Automatic control solution detection

Functions	• Large, easy to read backlit display • Test strip eject button • 7, 14, 30, 60, and 90 day averaging • Pre (AC) and post (PC) meal tagging • Memory bank holds 1000 tests with date and time • Automatic glucose control detection • Results can be downloaded to the 4SURE Diabetes Manager Software (via Bluetooth or USB) • Automatically switches off after 2 minutes of being idle
Blood glucose test strip expiry date	24 months from date of manufacture; opening of vial has no impact on expiration date.
Suitable for	• Drivers – Please follow DVLA guidelines for driving with diabetes[9] • Diabetes in pregnancy – Please follow NICE guidelines "Diabetes in pregnancy: management from preconception to the postnatal period"[10] • Neonatal use (glucose testing only)

Blood Glucose Test Strips



1+2: Individual HCT level is detected by touch
3+4: Blood sample is detected and measured

3. ISO 15197:2013 / EN ISO 15197:2015

The International Organization for Standardization (ISO) is recognized as the largest developer and publisher of International Standards. ISO 15197:2013 / EN ISO 15197:2015 specifies the requirements for the accuracy of *in vitro* glucose monitoring systems that measure glucose concentration in blood samples.[7]

Table 2: ISO acceptance criteria

Parameter	ISO 15197:2013/ EN ISO 15197: 2015
Glucose concentrations	
• Low glucose concentration	< 5.55 mmol/L
• High glucose concentration	≥ 5.55 mmol/L
System accuracy	
• Acceptable bias from reference value for lower target glucose levels	± 0.83 mmol/L
• Acceptable bias from reference value for higher target glucose levels	± 15%
• Percentage of values that need to fall within this bias	95%
• Percentage of values that need to fall within the consensus error grid zones A and B	99%
Influence quantification	
Interference Testing	
• Acceptable bias between control and sample containing potential interferent for low glucose levels	± 0.55 mmol/L
• Acceptable bias between control and sample containing potential interferent for high glucose levels	± 10%
Packed Cell Volume Evaluation	
• Acceptable bias between control and middle level packed cell volume for low glucose levels	± 0.55 mmol/L
• Acceptable bias between control and middle level packed cell volume for high glucose levels	± 10%
User performance evaluation	
• Acceptable bias from reference value for lower target glucose levels	± 0.83 mmol/L
• Acceptable bias from reference value for higher target glucose levels	± 15%
• Percentage of values that need to fall within this bias	95%

4. Method

System accuracy and measurement precision were tested and evaluated by an external party, "*Institut für Diabetes-Technologie Forschungs- und Entwicklungs-gesellschaft mbH an der Universität Ulm (IDT)*", between November 2017 and January 2018. The effect of influence quantities and user performance was tested and evaluated by the manufacturer.

4.1. Accuracy Evaluation

A diverse study population of 113 patients were recruited, from which capillary whole blood samples were taken. 600 glucose values were obtained and per ISO 15197:2013 / ISO EN15197:2015 guidelines, 3 lots of test strips were used in the study. The laboratory reference instrument used in the study was Cobas Integra® 400 plus.

4.2. Measurement Precision

4.2.1. Measurement Repeatability

Measurement repeatability is evaluated by a series of measurements (at least 10) using the same blood sample, meter, and test strip lot. Measurement repeatability was tested using 5 venous blood samples and strips from 3 reagent system lots. For each reagent system lot, test procedures were performed with 10 meters and each of the 5 venous samples with defined glucose concentrations. At least 10 measurements have been performed with each combination of meter, reagent lot, and sample. For each reagent system lot, measurements of a single sample were performed within one day. Measurement repeatability of each reagent system lot was assessed by calculating the coefficient of variation (CV) and the standard deviation (SD) for each blood glucose concentration interval.

4.2.2. Intermediate Measurement Precision

In order to measure the intermediate measurement precision of the 4SURE Smart BGMS, a control solution was used with 3 different glucose concentration intervals. 30 tests were carried out using test strips from 3 different lots. For each reagent system lot, test procedures were performed within 10 days with 10 meters on each of the 3 samples (glucose concentration intervals).

4.3. Influence Quantification

4.3.1. Packed Cell Volume Evaluation

To evaluate HCT effects on glucose measurements obtained using the 4SURE Smart BGMS, venous whole blood samples were obtained. 8 hematocrit levels (varying from 0 to 70%) were tested at 3 target glucose concentrations (1.7 - 2.8 mmol/L, 5.6 - 8.0 mmol/L, and 15.6 – 23.3 mmol/L). In total, 24 hematocrit/glucose samples were prepared and tested with test strips from 3 different reagent lots. The laboratory reference instrument used was YSI-2300.

4.3.2. Interference Testing

Venous blood samples were taken from healthy subjects. 2 pools of venous blood were created: one with blood glucose concentrations of approximately 4.1 mmol/L and the other one with blood glucose concentrations of approximately 18.15 mmol/L. 24 potential

interfering substances were tested (in accordance with guidelines of the Interference testing in clinical chemistry; Approved Guideline – 2nd edition). Each substance was measured once, using 10 meters and 3 reagent lots of test strips. The laboratory reference instrument used was YSI-2300.

4.4. User Performance Evaluation

160 lay persons (diabetic patients) were asked to use the 4SURE Smart BGMS after having read the instructions for use and the owner's manual. The 4SURE Smart results were then compared to Cobas C311 reference method results.

5. Results

5.1. Accuracy Testing

The table below shows how often 4SURE Smart BGMS achieves targets within ISO 15197:2013 / EN ISO 15197:2015 acceptance criteria.[11]

Table 3: Accuracy results

Glucose level	**Results within ± 0.83 mmol/L of laboratory results**
Low glucose concentration < 5.55 mmol/L	154/156 (98.72%)
Glucose level	**Results within ± 15% of laboratory results**
High glucose concentration ≥ 5.55 mmol/L	442/444 (99.55%)
Glucose level	**Results within ± 0.83mmol/L and within ± 15% of laboratory results**
2.22 – 25.3 mmol/L	596/600 (99.33%)

Note: Total of 3 different reagent system lots.

99.33% of all test results fell within ± 0.83 mmol/L (for low glucose values) and ± 15% (high glucose values) of laboratory test results *versus* the 95% ISO acceptance criteria. 4SURE Smart BGMS therefore surpasses the ISO norm.

5.1.1. ISO Bias Plot[11]

The difference between each individual BGMS reading and its corresponding Cobas Integra® 400 plus glucose reference concentration is shown in the ISO bias plot below.

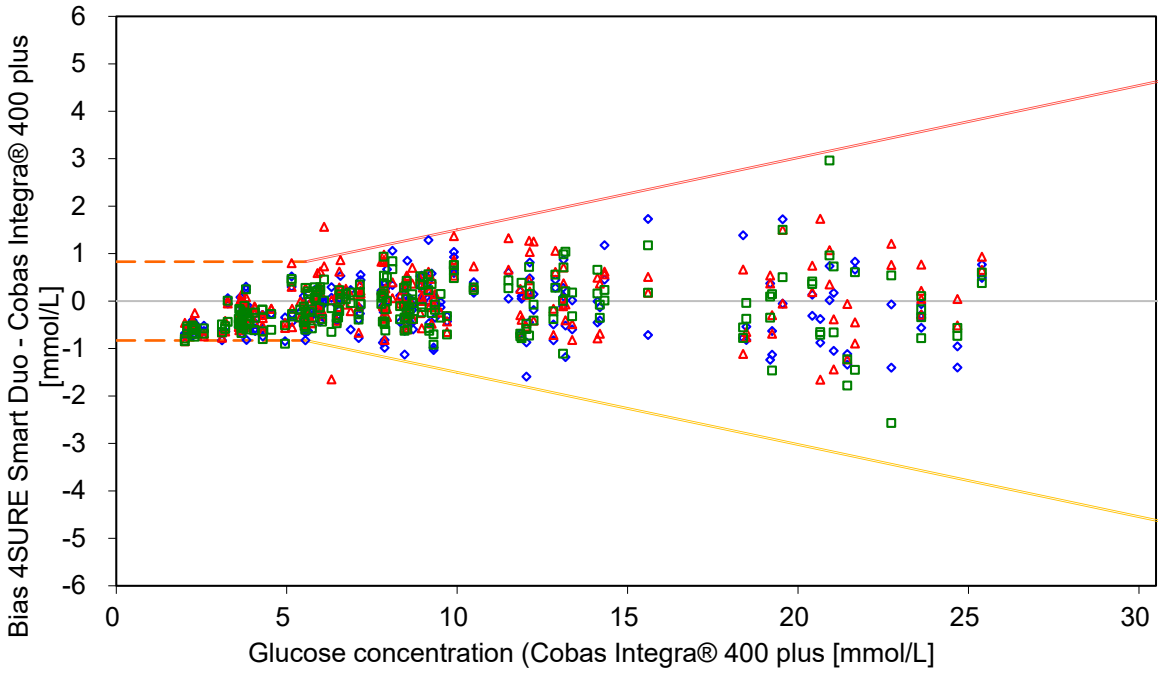


Figure 2: Absolute differences between 4SURE Smart BGMS and Cobas Integra® 400 plus

The mean bias (over 3 system lots) from laboratory results is - 0.1 mmol/L for low glucose values and - 3.37% for high glucose values.

5.1.2. Consensus Error Grid

The consensus error grid (CEG) shows the correlation between 4SURE Smart measurements and Cobas Integra® 400 plus measurements. It is divided into five zones, signifying the estimated degree of risk posed by the incorrect measurement.[12]

Table 4: CEG zones, estimated degree of risk

Risk level / CEG zone	Estimated degree of risk	# of points	% result in zone
A	No effect on clinical action	598	99.67%
B	Altered clinical action – little or no effect on clinical outcomes	2	0.33%
C	Altered clinical action – likely to affect clinical outcomes	0	0.00%
D	Altered clinical action – could have significant medical risk	0	0.00%
E	Altered clinical action – could have dangerous consequences	0	0.00%

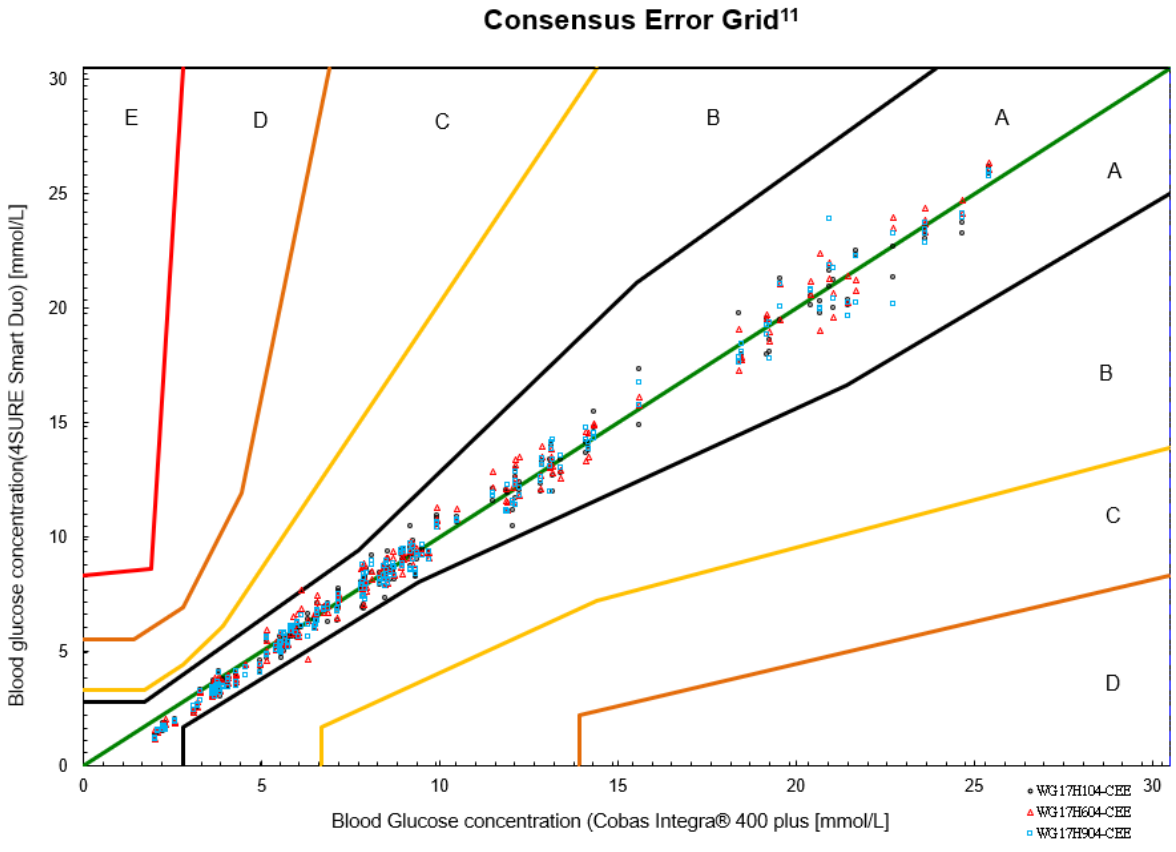


Figure 3: Consensus Error Grid for 4SURE Smart results – Cobas Integra 400plus

100% of test results fell into zone A and B of the consensus error grid (598 test results in zone A and 2 results in zone B), *versus* 99% ISO acceptance criteria.

4SURE Smart BGMS shows 99.33% accuracy.
100% of the individual glucose values measured fell within zones A and B of the CEG.[11]
Therefore, the system surpasses ISO norms.

5.2. Measurement Precision

Measurement precision consists of measurement repeatability and intermediate measurement precision. ISO 15197:2013 / EN ISO 15197:2015 does not specify acceptance criteria for measurement precision. The following acceptance criteria are generally accepted as industry standards:

- Standard deviation (SD) ± 0.25 mmol/L at glucose concentration < 5.55 mmol/L
- Coefficient of Variation (CV) ± 5% at glucose concentrations ≥ 5.55 mmol/L

5.2.1. Measurement Repeatability

The measurement repeatability of a system is defined as the agreement between measured quantities, obtained by a series of measurements over a short period of time under specified conditions. Standard deviation (SD) and coefficient of variation (CV) were calculated to assess measurement repeatability.[13]

Table 5: Measurement repeatability

Blood glucose concentration (mmol/L)	1.7 – 2.8	2.9 – 6.1	6.2 – 8.3	8.4 – 13.9	14.0 – 22.2
Mean BGMS measurement results (mmol/L]	1.5	4.0	7.3	12.3	17.3
SD (mmol/L)	0.12	0.13	0.17	0.19	0.26
95 % confidence interval for SD (mmol/L)	0.11 to 0.14	0.11 to 0.15	0.16 to 0.21	0.17 to 0.23	0.22 to 0.29
CV (%)	7.8	3.2	2.4	1.6	1.5
Variance (mmol/L²)	0.25	0.29	0.55	0.68	1.16

Note: Results of 3 reagent system lots.

5.2.2. Intermediate Measurement Precision

The intermediate measurement precision of a system is defined as the agreement between measured quantities, obtained by a series of measurements over an extended period of time under specified conditions. The intermediate measurement precision of each reagent system lot was assessed by calculating the CV and the SD for each blood glucose concentration interval.[14]

Table 6: Intermediate measurement precision

Blood glucose concentration (mmol/L)	1.7 – 2.8	5.3 – 8.0	15.5 – 23.3
Mean BGMS measurement results (mmol/L)	2.4	7.4	17.9
SD (mmol/L)	0.12	0.17	0.37
95 % confidence interval SD (mmol/L)	0.11 to 0.13	0.16 to 0.18	0.34 to 0.40
CV [%]	4.9	2.2	2.1

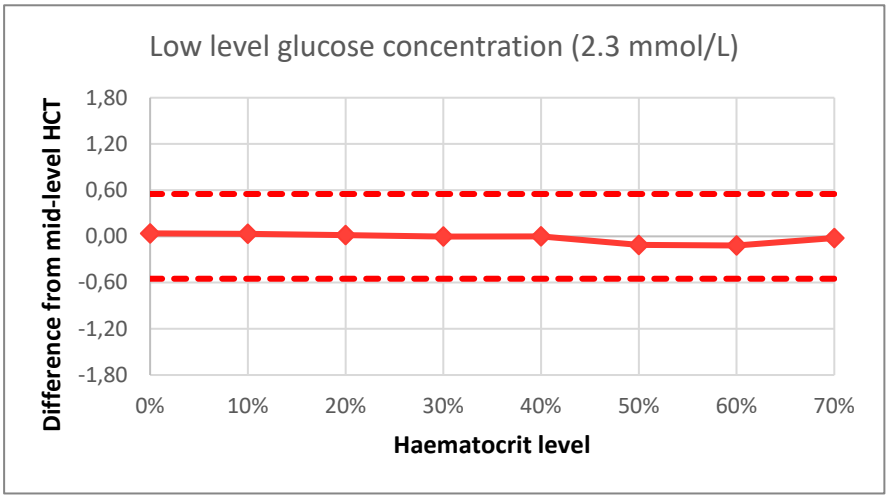
Note: Results of 3 reagent system lots.

Considering the overall low SD and CV values,
none of the evaluated components showed to have a relevant influence on the measurement results.[13,14]

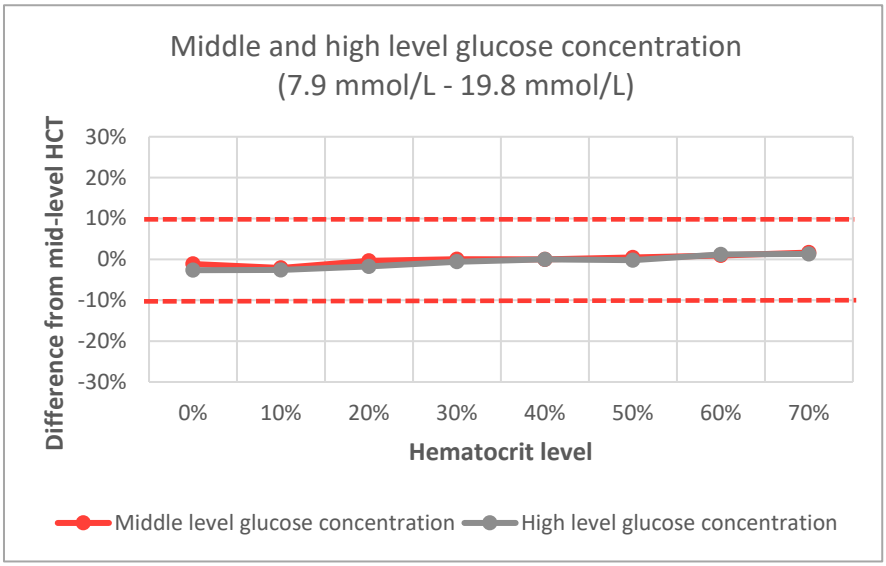
5.3. Influence Quantification

5.3.1. Packed Cell Volume or HCT Evaluation

Prevalence of HCT variation is usually underestimated by physicians and diabetes nurse educators and is also subject to seasonal variation.[15] HCT levels can interfere with glucose readings when using self-testing blood glucose meters, therefore EN ISO 15197:2015 describes strict acceptance criteria for packed cell volume evaluation (see chapter 4 of this paper). 42% (± 2%) is considered a normal hematocrit level,[7] for all glucose levels mid-level HCT samples were prepared with an hematocrit level of 40%. The below graphs show the difference between the average measured value at each HCT volume level and the average measured value at the mid-level HCT when using the 4SURE Smart BGMS.[16]



ISO Acceptance Criteria (± 0.55 mmol/L)



ISO Acceptance Criteria (± 10%)

4SURE Smart BGMS accurately measures glucose in whole blood with HCT levels ranging from 0 to 70%.[16]

5.3.2. Interference Testing

ISO 15197:2013 / EN ISO 15197:2015 lists 24 substances that may be present in the blood of intended users and are known to interfere with glucose measurements.[7] Table 7 gives an overview of the tested substances that do not interfere with the test strip either:[17]

- Within and beyond the therapeutic or physiologic concentration range (concentration tested)
- Within the therapeutic or physiologic concentration range (interference observed at limited concentration), indicated in the table by an asterisk (*)

Table 7: Interference testing results

Substance	Therapeutic / physiologic concentration range (mg/dL)*	Concentration tested (mg/dL)*	Bias with glucose 2.8 to 5.5 mmol/L (mmol/L)	Bias with glucose 13.9 to 19.4 mmol/L (%)
Salicylic Acid	10 – 30	60	0.44	5.34%
Bilirubin (Unconjugated)	0 – 2	40	0.50	8.39%
Cholesterol	300	500	-0.22	-0.51%
Creatinine	1.7	30	0.22	5.20%
Galactose	< 5	1000	-0.17	3.25%
Gentisic Acid	0.2 – 0.6	2	0.22	2.29%
Hemoglobin (Hemolysis Method)	2.5	500	0.44	7.38%
Heparin (Li)	35 – 100 U/dL	6800 U/dL	-0.39	2.51%
Heparin (Na)	35 – 100 U/dL	6800 U/dL	-0.33	2.08%
Ibuprofen	1 – 7	55	-0.33	1.34%
Icodextrin	1200	2000	0.28	6.38%
Maltose	N/A	1000	0.33	-1.08%
Tolbutamide	4.32 – 24	64	0.33	-1.85%
Acetaminophen (Paracetamol)*	0.45 – 3	20	0.38	8.93%
Ascorbic acid*	2.0	5.0	0.50	8.23%
Dopamine*	0.03	2.5	0.22	8.94%
Levo – Dopa*	0.02 – 0.28	2.1	0.22	5.21%
Methyl – Dopa*	0.1 – 0.5	1.25	0.17	3.42%
Tolazamide*	2 – 2.5	20	0.42	5.71%
Uric acid*	2 – 8	10	0.45	8.52%
Xylose*	N/A	5.0	0.44	5.58%
Lipemic Samples* (Triglycerides)	30 – 300	3000	0.38	4.74%

*Substance concentrations above the "concentration tested" may lead to biases in the interferent sample above 0.55 mmol/L (for low glucose values) or above 10% (for high glucose values). The concentration tested is therefore also the limiting concentration.[17]

The use of K3EDTA and K2EDTA as an anticoagulant for storing whole blood samples leads to interference in glucose readings. Therefore, the use of Heparin is recommended.[17]

Table 8: Anticoagulants for storing whole blood samples

Substance	Limiting concentration (mg/dL)	Concentration of blood drawing tube (mg/dL)	Bias with glucose 2.8 to 5.5 mmol/L (mmol/L)	Bias with glucose 13.9 to 19.4 mmol/L (%)
K3EDTA	< 175.5	175.5	-0.33	-8.22%
K2EDTA	< 180	180	-0.28	-7.34%

The use of Pralidoxime Iodide and Reduced Glutathione may produce elevated glucose results.[17]

Table 9: Substances leading to interference in glucose results when used within therapeutic concentration range

Substance	Concentration tested (mg/dL)	Therapeutic / physiologic concentration range (mg/dL)	Bias with glucose 2.8 to 5.5 (mmol/L)	Bias with glucose 13.9 to 19.4 mmol/L(%)
Pralidoxime Iodide	> 5.0	~ 10 (i.v. Dose 500 mg)	-0.39	8.14%
Reduced Glutathione	24.25 – 32.2	30	0.22	8.20%

All substances listed by ISO 15197:2013 / EN ISO 15197:2015 have been tested and 21 of them were found not to interfere with the performance of the system at physiological or therapeutic levels.[17]

5.4. User Performance Evaluation

BGMS systems are meant to be used both at the clinic by healthcare professionals and at home by the patient and should, therefore, be easy to use. A user performance evaluation was done to assess ease of use. The table below shows 98.75% of 4SURE Smart BGMS test results achieve targets within ISO 15197:2013 / EN ISO 15197:2015 acceptance criteria (95% of all values should fall within ± 0.83 mmol/L (for low glucose values) or ± 10% (for high glucose values)) when comparing lay patient test results to reference method test results.

Table 10: Accuracy results for glucose < 5.55 mmol/L[18]

Tested sites	Difference within ± 0.28 mmol/L	Difference within ± 0.56 mmol/L	Difference within ± 0.83 mmol/L
Fingertip	26/43 (60.5%)	37/43 (86%)	43/43 (100%)
Palm	27/42 (64.3%)	41/42 (97.6%)	42/42 (100%)
Forearm	31/42 (73.8%)	39/42 (92.9%)	42/42 (100%)
Upper arm	29/42 (69.0%)	38/42 (90.5%)	41/42 (97.6%)

Table 11: Accuracy results for glucose < 5.55 mmol/L[18]

Tested sites	Difference within ± 5%	Difference within ± 10%	Difference within ± 15%
Fingertip	59/117 (50.4%)	102/117 (87.2%)	115/117 (98.3%)
Palm	49/118 (41.5%)	92/118 (78.0%)	118/118 (100%)
Forearm	43/118 (36.4%)	84/118 (71.2%)	115/118 (97.5%)
Upper arm	49/118 (41.5%)	87/118 (73.7%)	116/118 (98.3%)

98.75% of all test results are within ISO 15197:2013 / EN ISO 15197:2015 acceptance criteria.[18]
Therefore, 4SURE Smart BGMS surpasses the ISO norms.

6. Conclusion

Clinical data shows that 4SURE Smart BGMS achieves targets within ISO 15197:2013 / EN ISO 15197:2015 accuracy acceptance criteria for 99.33% of test results *versus* the 95% ISO norm.[11] When the same test is performed by lay diabetic patients, 4SURE Smart BGMS still achieves 98.75% of test results within ISO 15197:2013 / EN ISO 15197:2015 acceptance criteria *versus* the 95% ISO norm.

When assessing measurement repeatability and intermediate measurement precision, the calculated standard deviation was within ± 0.25 mmol/L for low glucose concentrations and the coefficient of variation was within ± 5% for high glucose concentrations. For measurement repeatability, this means there is very little variation in measurements when testing the same blood sample with different meters and test strip combinations within 1 day. The overall low standard deviation and coefficient of variation in intermediate measurement precision indicate that, also when testing glucose control solution, there is very little variation between measurements with different meters and test strip combinations spread over 10 days.

The system is safe to be used with HCT levels varying from 0 to 70%. 21 substances out of the list of 24 "possible interfering substances" from ISO 15197:2013 / EN ISO 15197:2015 can be used, when used within therapeutic or physiologic concentration range, without interfering with blood glucose measurements.

The clinical data exceeds all rigorous accuracy criteria defined in ISO 15197:2013 / EN ISO 15197:2015. Therefore, we may conclude that the 4SURE Smart BGMS is accurate, precise, and easy to use.

7. References

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