BLOOD GLUCOSE METERS

ACCURACY REQUIREMENTS

International Standard ISO 15197:2013
(Second Edition 15/05/2013)

In vitro diagnostic test systems –
Requirements for blood-glucose monitoring systems
for self-testing in managing diabetes mellitus.

GlucoMen®

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CONTENTS

INTRODUCTION

New accuracy criteria for blood glucose meters have been published in the EN ISO 15197:2013 guidelines.

The purpose of this document is to clearly explain the key requirements of the new international standard. It aims to help NHS decision makers to make informed decisions for the well being of people with diabetes.

For each main section there is a brief summary of how the original ISO 15197:2013 document describes the general requirements, study design, and required format for presentation of results in order to prove compliance. In order to illustrate the correct presentation, GlucoMen Areo ISO evaluation data is included.

Section 6 describes the latest selection criteria that are being used to choose blood glucose monitoring systems for people with diabetes, arranged in terms of accuracy, patient desired features, and patient support.

The new guidelines state that:

'Medical experts involved in the development of this edition believed that better performing meters would result in more accurate insulin dosing and therefore should lead to better patient outcomes'.

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SECTION 1: System Accuracy Evaluation

General Requirements of the System Accuracy Evaluation

System accuracy is evaluated by comparing test results achieved with the meter to laboratory reference values. The glucose reference value shall be the average of at least two measurements, using a procedure that conforms to the traceability requirements of ISO 17511.

1.1 Study Design

Six hundred blood glucose tests must be carried out, with **one hundred** patients and duplicate tests performed on **three different lots of test strips** (i.e. 200 tests are performed on each of 3 lots). The glucose concentrations must be distributed to span the measuring range of the blood glucose meter, distributed as shown below:

Percentages of Samples of Each Glucose Concentration (mmol/L)						
≤ 2.77	> 2.77 - 4.44	> 4.44 - 6.66	> 6.66 -11.10	> 11.10 -16.65	> 16.65 - 22.20	> 22.20
5%	15%	20%	30%	15%	10%	5%

Six GlucoMen Areo meters were used so that two meters were used for each of the three lots of test strips.

1.2 System Accuracy Requirement A: Accuracy Plot

The minimum accuracy performance criteria are:

- At glucose levels < 5.55 mmol/L, 95% of results should be within ± 0.83 mmol/L of laboratory results
- At glucose levels ≥ 5.55 mmol/L, 95% of results should be within ± 15% of laboratory results

This must be applied to the three test strip lots separately, with a separate analysis and report for each.

1.3 Presentation of Results

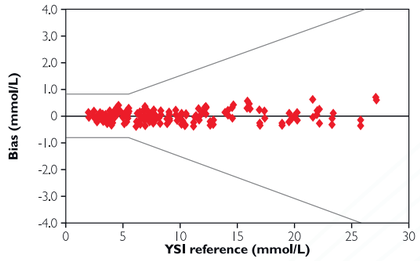
Study results must be presented in the following formats for each of the three test strip lots:

- A system accuracy plot (difference plot)
- A table showing the percentage of results falling within accuracy intervals

Study results for three lots of GlucoMen Areo test strips are shown opposite **(page 5)**.

GlucoMen Areo Accuracy Plots and Tables for Three Test Strip Lots

Lot 1: H1S1308001



Accuracy results for glucose < 5.55 mmol/L

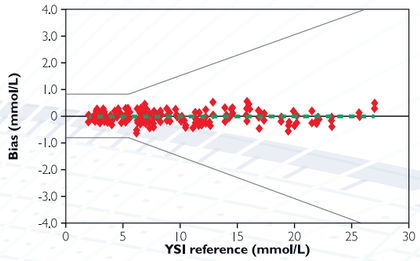
Within ± 0.28 mmol/L	Within ± 0.56 mmol/L	Within ± 0.83 mmol/L
46 (66) **69.7%**	65 (66) **98.5%**	66 (66) **100%**

Accuracy results for glucose ≥ 5.55 mmol/L

Within ± 5%	Within ± 10%	Within ± 15%
112 (134) **83.6%**	133 (134) **99.3%**	134 (134) **100%**

Within ± 0.83mmol/L and ±15%	
200/200	**100%**

Lot 2: H1S1308002



Accuracy results for glucose < 5.55 mmol/L

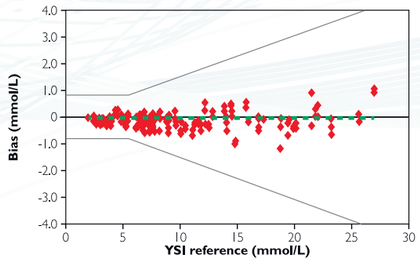
Within ± 0.28 mmol/L	Within ± 0.56 mmol/L	Within ± 0.83 mmol/L
48 (66) **72.7%**	**66** (66) **100%**	66 (66) **100%**

Accuracy results for glucose ≥ 5.55 mmol/L

Within ± 5%	Within ± 10%	Within ± 15%
112 (134) **83.6%**	131 (134) **97.8%**	133 (134) **99.3%**

Within ± 0.83 mmol/L and ±15%	
199/200	**99.5%**

Lot 3: H1S1308003



Accuracy results for glucose < 5.55 mmol/L

Within ± 0.28 mmol/L	Within ± 0.56 mmol/L	Within ± 0.83 mmol/L
52 (66) **78.8%**	65 (66) **98.5%**	66 (66) **100%**

Accuracy results for glucose ≥ 5.55 mmol/L

Within ± 5%	Within ± 10%	Within ± 15%
93 (134) **69.4%**	129 (134) **96.3%**	134 (134) **100%**

Within ± 0.83 mmol/L and ±15%	
200/200	**100%**

Results: 100% of results are within 0.83 mmol/L and 99.8% are within ±15% for combined lots

Conclusion: GlucoMen Areo exceeds system accuracy requirement of 95%

SECTION 1: System Accuracy Evaluation

1.4 System Accuracy Requirement B: Consensus Error Grid

The minimum accuracy performance criteria are:

- 99% of results must be within zones A & B of the Consensus Error Grid (CEG) for type 1 diabetes *(figure 1)*

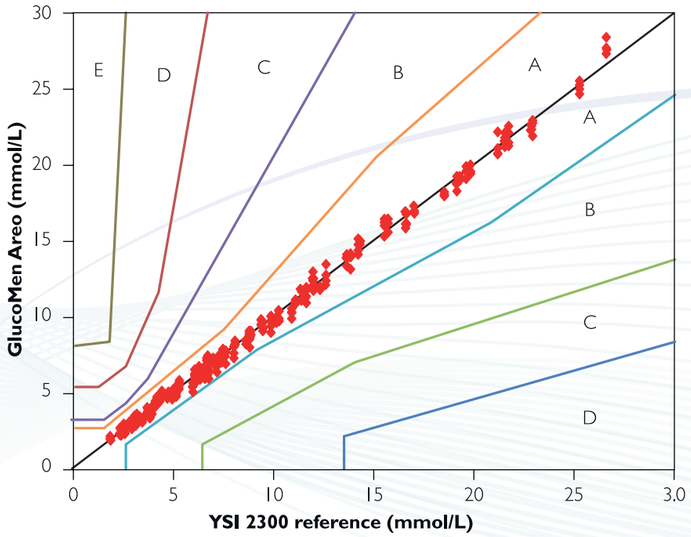
1.5 Presentation of Results

Study results from the 3 test strip lots must be combined before analysis and reporting within a Consensus Error Grid.

Zone A	No effect on clinical action
Zone B	Altered clinical action – little or no effect on clinical outcome
Zone C	Altered clinical action – likely to affect clinical outcome
Zone D	Altered clinical action – could have significant medical risk
Zone E	Altered clinical action – could have dangerous consequences

The grid is divided into zones signifying the degree of risk posed by the incorrect measurement (above).

Figure 1 – Consensus Error Grid for GlucoMen Areo Evaluation



	Zone A	Zone B	Total
Lot 1	200	0	200
Lot 2	200	0	200
Lot 3	200	0	200
Total	**600**	**0**	**600**
%	100%	0%	100 %

Results: 100% of results are within zone A of the Consensus Error Grid

Conclusion: GlucoMen Areo exceeds system accuracy requirement of 99% within zones A and B

SECTION 2: Precision and Repeatability Evaluation

General Requirements of the Precision and Repeatability Evaluation

Repeatability is evaluated by a series of measurements using the same blood sample, meter and test strip lot.

2.1 Study design

Ten tests are performed on each of **ten** meters, using the same blood sample **(100 tests in total)**. This is repeated using **five** blood glucose samples with concentrations ranging from low to high. Each meter is assigned a lot of test strips and a total of **three** lots must be used during the study.

2.2 Requirement: Precision and Repeatability Evaluation

ISO15197:2013 doesn't specify a separate acceptability criteria for precision. The manufacturer must establish acceptance criteria within the study protocol. In the GlucoMen Areo evaluation the industry standard was applied.

- 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

2.3 Presentation of Results

The average glucose value for each sample must be reported along with standard deviation (SD) and coefficient of variation (CV) for each glucose concentration ≥ 5.55 mmol/L, and standard deviation (SD) for each glucose concentration < 5.55 mmol/L.

		Level 1	Level 2	Level 3	Level 4	Level 5
Lot 1	Mean	2.9	4.1	7.3	12.4	18.9
	SD	**0.122**	**0.122**	0.161	0.294	0.317
	CV	NA	NA	**2.2%**	**2.4%**	**1.7%**
Lot 2	Mean	3.0	4.2	7.3	12.5	18.9
	SD	**0.117**	**0.111**	0.178	0.283	0.294
	CV	NA	NA	**2.4%**	**2.2%**	**1.6%**
Lot 3	Mean	2.9	4.0	7.4	12.4	18.8
	SD	**0.111**	**0.111**	0.172	0.272	0.344
	CV	NA	NA	**2.4%**	**2.2%**	**1.8%**
All Lots	Mean	2.9	4.1	7.3	12.4	18.9
	SD	**0.117**	**0.111**	0.172	0.283	0.317
	CV	NA	NA	**2.3%**	**2.3%**	**1.7%**

Conclusion: GlucoMen Areo exhibits excellent precision and test repeatability at all levels tested

SECTION 3: Haematocrit Interference Evaluation

Background – The significance of haematocrit as a source of error

Varying haematocrit is a potential source of error in blood glucose monitoring.

Abnormal haematocrit levels can interfere with glucose readings of patient self-testing blood glucose meters and are potentially a very significant source of inaccuracy.

How commonly will haematocrit levels vary from the normal level of approximately 42% ?

A recent investigation, analysing data from 15,108 community patients has reported haematocrit ranging from 20 to 60%. [1]

Such deviations from normal haematocrit levels of approximately 42% can be induced by lifestyle interventions (e.g. smoking or prolonged exercise), environmental conditions (e.g. altitude or seasonal variations), demographic factors (e.g. age) and disease and drug related conditions (e.g. haematological disorders, hypermenorrhea, pregnancy or renal disease). [2,3]

Within subject variability also exists, indicated by a 15% relative change. [4]

Why can varying haematocrit dramatically affect a blood glucose test ?

Haematocrit that is lower than normal can lead to overestimation of glucose values and haematocrit that is higher than normal can lead to underestimation of glucose values. The impact of abnormal haematocrit on blood glucose testing may be explained by a change in diffusion kinetics, and / or increased packed red cell volume and displacement of plasma volume leading to insufficient plasma volume for accurate testing.

The impact of abnormal haematocrit will vary depending upon the technology of the blood glucose monitoring system.

3.1 Study Design

Evaluation of haematocrit effect must be carried out using blood samples:

- At a minimum of 5 haematocrit levels
- At each of 3 blood glucose levels *(table 3.1)*
- Using 3 different lots of test strips

At least 30 tests are carried out on each combination of haematocrit and glucose level, 10 tests with each test strip lot.

Table 3.1 – Typical glucose range for haematocrit evaluation

Glucose concentration	Glucose range (mmol/L)	Areo Test value (mmol/L)
Level 1	1.7 - 2.8	2.2
Level 2	5.3 - 8.0	7.2
Level 3	15.6 - 23.3	16.7

3.2 Requirement: Haematocrit Interference Evaluation

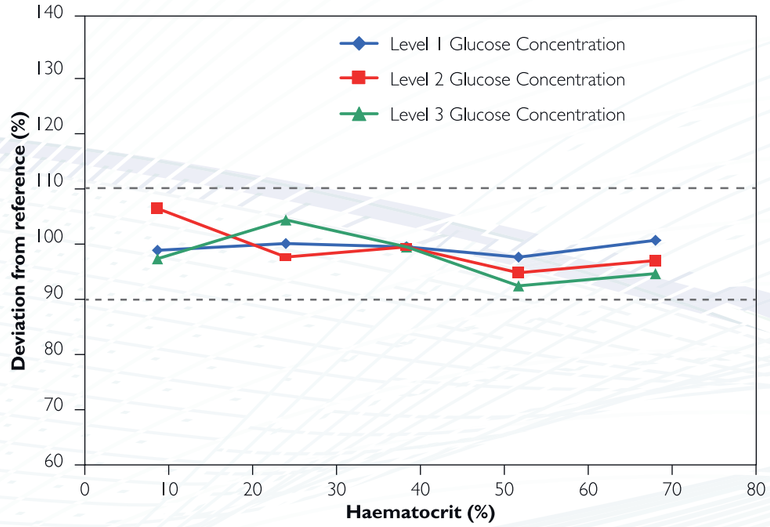
For all haematocrit levels within the declared acceptable range the difference between the average measured value and the mid-level value of 42% ± 2% shall not exceed:

- 0.55 mmol/L at glucose levels <5.55 mmol/L, or
- ± 10% at glucose levels ≥5.55 mmol/L

3.3 Presentation of Results

A graph showing the difference between the average glucose test result at each haematocrit level and the average glucose test result at the mid-level haematocrit is required for each glucose level. The maximum allowable deviations (10%) are identified with a dashed line.

GlucoMen Areo Haematocrit Interference Evaluation



Results: GlucoMen Areo exhibits an haematocrit interference effect of less than 10% at all levels

Conclusion: GlucoMen Areo exceeds ISO 15197:2013 requirements

1. Lyon ME, Lyon AW. Patient acuity exacerbates discrepancy between whole blood and plasma methods through error in molality to molarity conversion: "Mind the gap!". Clin Biochem. 2011;44(5-6):412–7.
2. Takubo T, Tatsumi N. Reference values for hematologic laboratory tests and hematologic disorders in the aged. Rinsho Byori. 2000;48(3):207–16.
3. Macdougall IC, Ritz E. The Normal Haematocrit Trial in dialysis patients with cardiac disease: are we any the less confused about target haemoglobin? Nephrol Dial Transplant. 1998;13(12):3030–3.
4. Thirup P. Haematocrit: within-subject and seasonal variation. Sports Med. 2003;33(3):231–43.

SECTION 4: User Performance Evaluation

General Requirements of the User Performance Evaluation

The user performance evaluation is designed to ensure that users can obtain accurate test results given only the instructions and training materials routinely provided with the meter.

It is required to be performed prior to placing a new blood glucose monitoring system into commercial distribution.

4.1 Study Design

- At least 100 lay persons with diabetes must participate in the study, representing different ages, genders and education levels
- No instructions, training, assistance, feedback or supplemental instructional materials are provided to participants
- The test results achieved by lay persons with the meter are compared with those measured by the laboratory reference method, using the same drop of blood (or separate sample taken within 5 minutes)
- An evaluation questionnaire must assess whether the users understood how to use the device correctly

Distribution of Participants (%) – GlucoMen Areo Study:

Male / Female	
Male	27
Female	73

Diabetes Type	
Type 1	7
Type 2	93

Level of Education	
School	64
Technical College	25
University	7
Post graduate	4

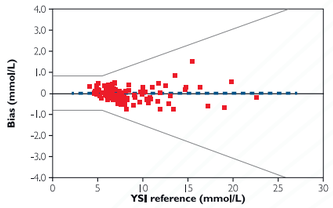
Age (years)	22 – 86 yrs
20 - 29	2
30 - 39	19
40 - 49	15
50 - 59	15
60 - 69	27
>70	22

4.2 User Performance Accuracy Criteria and Evaluation of Results Achieved

The study results shall be presented as a system accuracy plot (difference plot), **shown below.**

- At glucose levels < 5.55 mmol/L, 95% of results should fall within ±0.83 mmol/L of laboratory results
- At glucose levels ≥ 5.55 mmol/L, 95% of results should fall within ±15% of laboratory results

System Accuracy Plot for GlucoMen Areo User Performance Evaluation



Accuracy results for glucose < 5.55 mmol/L

Within ± 0.28 mmol/L	Within ± 0.56 mmol/L	Within ± 0.83 mmol/L
13 (20) **65**%	19 (20) **95**%	20 (20) **100%**

Accuracy results for glucose ≥ 5.55 mmol/L

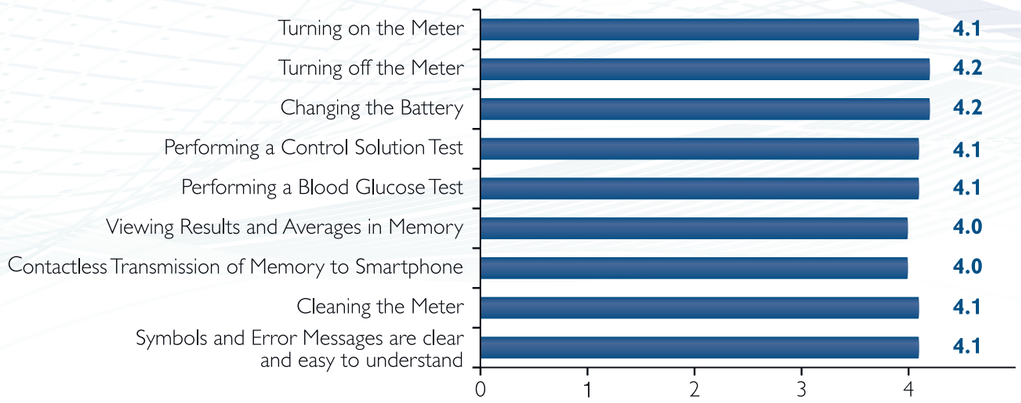
Within ± 5%	Within ± 10%	Within ± 15%
42 (80) **52.5**%	71 (80) 88.8%	79 (80) **98.8%**

4.3 Evaluation of Instructions for Use by Lay Users

A questionnaire is used to assess whether users understood how to use the meter correctly.

Participants indicate their degree of agreement with statements relating to the ease of use of the meter, on a scale of 1 to 5 (where 1 = strongly disagree; 3 = neutral; 5 = strongly agree).

Evaluation Questionnaire Results for GlucoMen Areo:



Equipped with only the meter and the user manual, lay people using GlucoMen Areo found each step of operation to be easy or very easy

SECTION 5: Testing for Endogenous & Exogenous Interfering Substances

General Requirements

ISO 15197:2013 lists a number of substances that could be present in the blood and have previously been found to interfere with a glucose measurement procedure.

5.1 Study Design

Evaluation of potentially interfering substances must be carried out at 2 glucose concentrations, one within 2.8 to 5.5 mmol/L and one within 13.9 to 19.4 mmol/L.

At least 10 meter tests are carried out on each sample to arrive at an average that is compared to the reference glucose value.

5.2 Performance Criteria – Interfering Substances

A substance is considered an interferent if the average difference between the test sample and the control sample exceeds :

- 0.55 mmol/L for the glucose concentration <5.55 mmol/L, or
- 10% for the glucose concentration ≥5.55 mmol/L

5.3 Presentation of Results – GlucoMen Areo Interference Testing (shown opposite)

Maltose Independence:
GlucoMen Areo test strips (Glucose Oxidase enzyme) react specifically with ß D-glucose and do not react with any other sugars that may be in the blood.

Lipaemic Samples:
Cholesterol up to 13.0 mmol/L and Triglycerides up to 38.0 mmol/L do not significantly affect test results.

Testing was carried out as described by the Clinical Laboratory Standards Institute CLSI – EP7 – P Vol. 6 No. 13. Interference testing in clinical chemistry.

Results: All 30 substances have been tested at two levels of glucose (3.3 mmol/L and 17.8 mmol/L) and found not to interfere with the performance of the system at physiological or therapeutic levels

GlucoMen Areo interference testing: Table of results

Substance Tested	Substance Concentration	Bias with Glucose 2.8 to 5.5 mmol/L	Bias with Glucose 13.9 to 19.4 mmol/L
Acetominaphen	10 mg/dL	0.23	-1.0%
L-DOPA	3 mg/dL	0.07	0.9%
Tolbutamide	25 mg/dL	-0.24	-2.0%
Dopamide	0.1 mg/dL	-0.30	-2.1%
Ibuprofen	40 mg/dL	-0.24	-3.6%
Acetylsalicylic acid	40 mg/dL	-0.32	-3.8%
Methyl-Dopa	15 mg/dL	-0.12	2.0%
Tetracycline	1.5 mg/dL	-0.31	0.3%
Ephedrine	0.05 mg/dL	-0.41	-5.0%
Mannitol	30 mg/dL	-0.29	-2.5%
Mannose	5.5 mg/dL	-0.53	-7.1%
Sorbitol	0.2 mg/dL	-0.30	-4.4%
Tolazamide	23 mg/dL	0.29	2.9%
Ascorbic acid	6 mg/dL	0.06	-0.4%
Maltose	50 mg/dL	-0.37	-8.0%
EDTA	0.5 mg/dL	-0.34	-5.3%
Lactose	25 mg/dL	-0.44	0.3%
Heparin	3000 U/L	-0.31	-1.5%
Maltotriose	240 mg/dL	-0.30	-0.9%
Maltotetraose	120 mg/dL	-0.38	-3.5%
Xylitol	0.12 mg/dL	-0.39	-3.3%
Xylose	30 mg/dL	-0.47	-3.2%
Gentisic acid	2 mg/dL	-0.17	-3.9%
Paralidoxime Iodide (PAM)	50 mg/dL	0.34	5.8%
Icodextrin	75 mg/dL	0.23	3.1%
Fructose	20 mg/dL	-0.35	-2.9%
Hemoglobin	200 mg/dL	-0.49	-6.2%
Creatinine	5 mg/dL	-0.26	-4.1%
Uric acid	15 mg/dL	-0.43	-3.0%
Cholesterol	200 mg/dL	-0.35	-4.3%
BILIRUBIN	30 mg/dL	-0.28	8.6%
triglyceride	500 mg/dL	0.21	8.8%
Galactose	15 mg/dL	-0.39	-4.8%
Glutathione	1.5 mmol/L	0.16	7.5%

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SECTION 6: Meter Selection Criteria

Meter Selection Criteria for Blood Glucose Monitoring Guidelines for People with Type 2 Diabetes

Checklist – use this table to compare meters under evaluation	GlucoMen Areo	Other
System accuracy plots for three separate strip lots	✓	
Consensus Error Grid	✓	
Haematocrit Interference Evaluation Data	✓	
User Performance Evaluation Data	✓	
Interference Testing Data	✓	
Test strip price guaranteed below £10 for three years	✓	
Patient review support at practice level	✓	
Free batteries	✓	
Attractive meter design	✓	
Large backlit display	✓	
Non deletable memory greater than 400 tests (Group 2 driver DVLA requirement)	✓	
Contactless download to Smartphones	✓	
No Coding Required	✓	
Test time less than or equal to 10 seconds	✓	
Sample size less than or equal to 0.5 microlitres	✓	
Finger pricker with lancet ejection	✓	
A 30G lancet or finer	✓	
Easy to handle test strip	✓	
Test strip ejector	✓	
UK based customer support helpline	✓	

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Notes

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