Evaluation of the FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System

Objectives: *To evaluate the performance of the Abbott Diabetes Care FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System against the performance requirements for blood glucose monitoring in ISO 15197:2013[1] in clinical and laboratory studies.*

Methods: *Accuracy and user performance in testing fresh capillary whole blood samples were assessed at two diabetes clinics. Results obtained with three lots of test strips were compared to plasma equivalent glucose values from the YSI analyser. Lay users were also asked to rate ease of use of the system via a questionnaire.*

Laboratory studies were performed at Abbott Diabetes Care to verify the performance of the FreeStyle Optium Neo system under varied test conditions.

Results: *Clinical accuracy of the FreeStyle Optium Neo system was demonstrated by comparing results from 186 blood samples (from 165 subjects), tested across 3 test strip lots by trained operators, to results obtained with the YSI analyser. Results met the system accuracy requirements of ISO 15197:2013:*

- 99.1% of results agreed within ± 15 mg/dL (0.83 mmol/L) of the reference values at glucose concentrations <100 mg/dL (5.55 mmol/L) and within ± 15% of the reference values at glucose concentrations ≥100 mg/dL (5.55 mmol/L)
- 100% of results were in Zones A and B of the Consensus Error Grid

Similarly, the accuracy requirements of the standard were met in the user performance (i.e. lay user) testing, with 97.9% of results within the accuracy criteria. The overall mean rating for the 174 subjects completing the ease of use questionnaire was 5.5 (out of 6), demonstrating that these users found the system easy to use.

In the laboratory studies, repeatability evaluation yielded standard deviations (SD) ≤2.7 mg/dL (0.15 mmol/L) at glucose concentrations <100 mg/dL (5.55 mmol/L) and coefficients of variation (CV) ≤3.5% at glucose concentrations ≥100 mg/dL (5.55 mmol/L). Intermediate precision assessment demonstrated SDs ≤3.3 mg/dL (0.18 mmol/L) at glucose concentrations <100 mg/dL (5.55 mmol/L) and CV of 3.1% at glucose concentrations ≥100 mg/dL (5.55 mmol/L). System results were not affected by high altitude (10000 feet, 3048 meters). Additional studies demonstrated that the system provided accurate results across the claimed haematocrit range (30 to 60%) and with 30 potentially interfering substances at high concentrations – biases observed were less than the criteria which trigger inclusion of the results in the product labelling per ISO 15197:2013.

Conclusions: *The clinical studies verify accuracy of the FreeStyle Optium Neo system for fingerstick capillary testing when compared to laboratory method results – accuracy in user performance testing and trained operator system accuracy evaluation met the requirements in ISO 15197:2013. The FreeStyle Optium Neo system had a high ease of use rating by first time users. Laboratory studies demonstrated that the system maintained accuracy in various challenging conditions that may be encountered in everyday home testing. These also demonstrated that influence conditions identified in ISO 15197:2013 (haematocrit & interfering substances) did not influence the system to such an extent that would require description of their effects in the product labelling in order to be compliant with ISO 15197:2013.*

Introduction

The FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System has been designed to meet the performance requirements introduced in the ISO 15197:2013 standard.[1] The FreeStyle Optium Neo system is designed to simplify patient testing and also provides features that can enhance their diabetes management, including Blood Glucose Trend Indicators and Insulin Dosing Guide. These additional features will not be discussed herein since the focus of this paper is the performance of the FreeStyle Optium Neo system in relation to ISO 15197:2013.

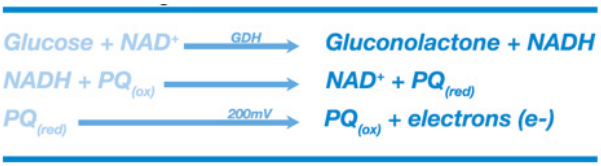
The test strips, branded as FreeStyle Optium, retain the TrueMeasure features of dual fill (end fill or top fill), fill trigger electrode and unique chemistry with low applied potential); the small sample volume requirement (minimum 0.6 µL); the short test time (5 seconds); the individual foil wrapping, designed to protect from exposure to moisture, chemicals or contaminants; and require no coding or calibration by the user. Use of the test strips with the FreeStyle Optium Neo system provides improved accuracy and reduced sensitivity to haematocrit[a], to meet the performance requirements introduced in ISO 15197:2013.

Technology

Measurement Principal

Glucose dehydrogenase (GDH-NAD), coenzyme nicotinamide adenine dinucleotide (NAD) and an electron mediator (phenanthroline quinone, PQ) are present on the working electrode of the test strip. Glucose in the blood sample is oxidised to gluconolactone by reaction with NAD, this oxidation is catalysed by GDH (*Figure 1*). The PQ reacts with the reduced coenzyme (NADH), thus reducing the mediator and returning the coenzyme to its oxidised state (NAD). The reduced mediator is oxidised at the working electrode, this produces a small electric current which is proportional to the concentration of glucose in the sample and is measured by the meter.

Figure 1. Reaction Scheme

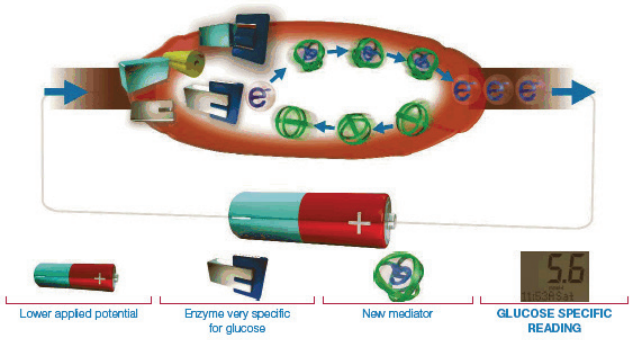


Lack of Interference

GDH can be used to perform electrochemical glucose measurements without direct interference by oxygen in the blood sample, thus reducing interfering effects caused by oxygen. Glucose Oxidase (GOX), the enzyme used in some other blood glucose monitoring system (BGMS), may react with oxygen to cause measurement errors.

Low potential measurements (*Figure 2*) can minimise interference by substances present in the blood sample. For an electrochemical reaction to occur, a potential (voltage) is applied between the working and reference electrodes. The larger the applied potential, the greater the number of interfering substances that can be oxidized at the working electrode and produce a false signal. The electron mediator (PQ) used in these test strips allows the electrochemical reaction to occur at low potential, so there is minimal interference with the test strip results from other substances.

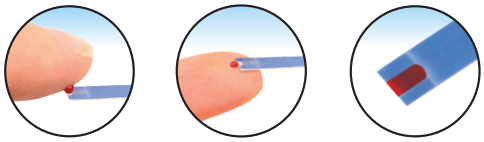
Figure 2. FreeStyle Optium Neo Measurement Principal



Dual Fill

The test strip retains the dual-fill feature that allows the user to apply blood to either the top or the end of the test strip (*Figure 3*). The blood is automatically drawn into the reaction area.

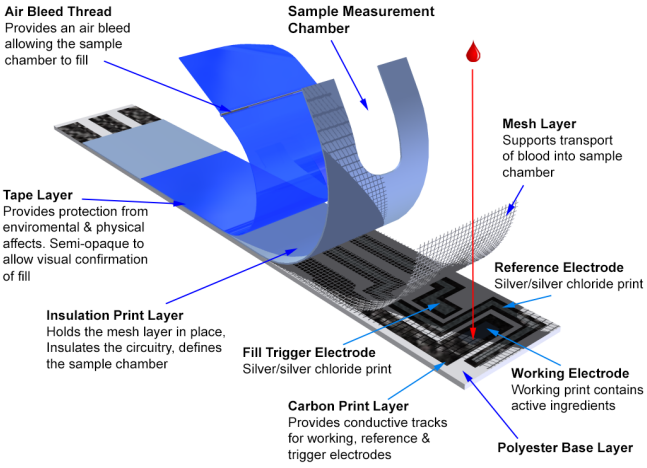
Figure 3. End fill or Top Fill Test Strip



Fill Trigger Electrode

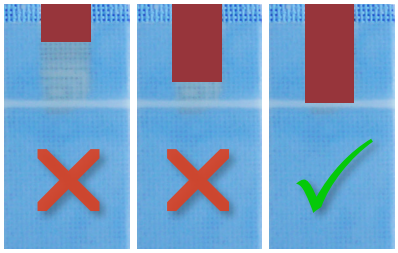
The test strip contains three electrodes (working, reference and fill trigger) – see *Figure 4*. The circuit between the fill trigger and the reference electrodes must be detected by the meter before the test will start. The completed circuit is only detected when the applied sample flows beyond the reference and working electrodes to contact the fill trigger electrode (*Figure 5*). This feature minimises errors due to insufficient sampling and reduces test strip waste. Upon application of sufficient sample, the test is automatically initiated.

Figure 4. Test Strip Architecture



[a] Compared to use of the test strips with the FreeStyle Optium system

Figure 5. Test Strip Only Starts When Sufficient Sample is Applied
Completed circuit only detected when sample reaches the trigger electrode



Summary of Features

The combination of the fill trigger electrode, the GDH-NAD chemistry with low applied electric potential and the dual fill design with visual confirmation of fill is the basis of TrueMeasure technology, designed to minimise errors from insufficient blood samples and interfering substances, allow easy sample application and thus protect the integrity of glucose testing data from preventable errors. Test strips are individually wrapped in foil packets to protect from exposure to moisture, chemicals or contamination.

In addition to the features described above, the FreeStyle Optium Neo system incorporates a number of enhancements to provide minimal sensitivity to haematocrit and high accuracy with the short (5 second) test time and no requirement for coding or calibration by the user. These features help to ensure compliance to performance requirements introduced in ISO 15197:2013 and also enhance the reliability of patient testing.

Performance Evaluation

This report details a comprehensive evaluation of the FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System. A multicentre clinical study was conducted to evaluate performance with fresh capillary whole blood. Additional laboratory studies were performed to verify performance claims under various testing conditions.

Comparative Methods

The YSI 2300 Stat Plus glucose analyser served as the comparative method in the clinical and laboratory studies. The YSI whole blood glucose results were multiplied by 1.12 to obtain plasma equivalent glucose values for comparison with the test strip results. The YSI glucose analyser has metrological traceability to NIST certified reference material.[2]

Statistical Analysis

All statistical analyses for the clinical studies were performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC). Passing and Bablok regression[3] was used to correlate meter results with comparative method values in the capillary clinical evaluation. Passing and Bablok regression analysis is recommended by the American Association of Bioanalysts[4] for method comparison (accuracy) studies. Mean absolute relative difference (MARD) between meter results and comparative method values was calculated to assess the mean absolute bias. Data were excluded from statistical analysis if (1) the drift between the first and second measurements of the comparative method was >4 mg/dL at glucose ≤100 mg/dL or >4% at glucose >100 mg/dL; (2) time exceeded the interval specified in the protocol (eg the BGMS and YSI tests on each sample must be completed within 20 minutes of sample collection); or (3) the data set was not complete (eg missing haematocrit level or YSI value). Laboratory study results were evaluated using JMP version 5.1 statistical software (SAS Institute) or SAS® version 9.2 or higher.

Clinical Study - Capillary (Fingerstick)

Materials & Method

Accuracy of the FreeStyle Optium Neo system was evaluated at two medical centres in the United States. 174 subjects were enrolled in the study. 9 subjects were excluded from the analysis due to protocol deviations, yielding 165 subjects. Samples from 21 of these subjects were modified to provide additional samples (186 samples in total) at low and high glucose concentrations for system accuracy analysis. Blood samples collected with an appropriate anticoagulant were spiked with a 0.9% saline solution containing a high concentration of glucose to prepare high glucose samples; the spiked samples were allowed to stand for at least 15 minutes before use to allow the added glucose to equilibrate between the plasma and red blood cells. To prepare low glucose samples, blood samples collected with an appropriate anticoagulant were incubated at 27 to 37 °C to allow glycolysis to occur.

Three test strip lots were used in the study; each sample was tested on 2 strip lots. Each strip lot tested per sample was tested once by the lay user (for user accuracy evaluation and ease of use survey) and in duplicate by the trained operator (for system accuracy evaluation). FreeStyle Optium Neo results were compared to results obtained on the YSI analyser.

Each of the 174 lay users completed a questionnaire rating ease of use topics after reading the instructions for use and performing a glucose test on their own. A scale of 1 to 6 was used, with 6 being the highest rating. An overall ease of use rating was obtained by averaging all responses. The age of the users ranged from 13 to 84 years. 51% were male & 49% were female. 56% had college or higher level of education. 28% had Type 1 diabetes and 72% had Type 2 diabetes.

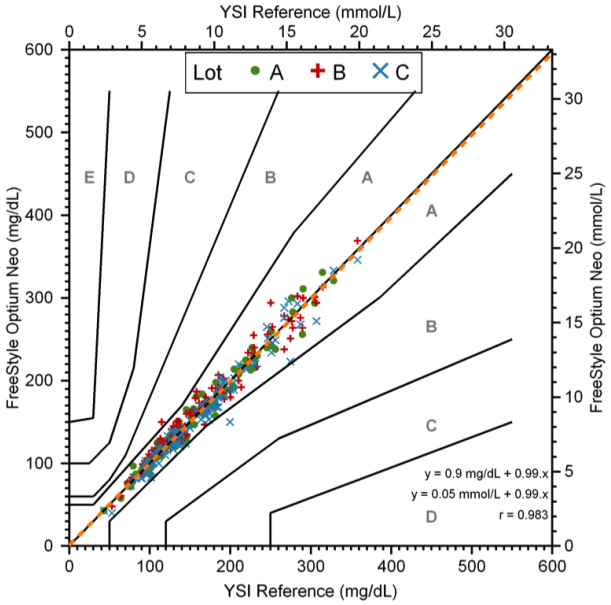
The methods used in the user performance evaluation & the system accuracy evaluation are based on those outlined in ISO 15197:2013.

Results – User Accuracy Evaluation & Ease of Use (Lay User)

The haematocrit range of the samples in this study was 25 – 51%, and the range of glucose concentrations was 43 – 358 mg/dL (2.4 – 19.9 mmol/L).

Excellent correlation was found between the FreeStyle Optium Neo system and the YSI analyser by regression analysis (r = 0.98, slope = 0.99, intercept = 0.9 mg/dL [0.05 mmol/L]) – see *Figure 6*. Overall the mean absolute relative difference (MARD) was 5.2%. Of the 330 test results (from 165 subjects), 328 (99.4%) were in Zone A (clinically accurate) and 2 (0.6%) were in Zone B (clinically acceptable) of the Consensus Error Grid[5] – see *Figure 6*.

Figure 6. Fingertip Accuracy – Consensus Error Grid & Regression Analysis



This study evaluating glucose values from fingertip capillary blood samples obtained by 165 lay users showed:

- 97.7% (43/44) of results were within ±15 mg/dL (0.83 mmol/L) of the reference values at glucose concentration <100 mg/dL (5.55 mmol/L)
- 97.9% (280/286) of results were within ±15% of the reference values at glucose concentrations ≥100 mg/dL (5.55 mmol/L).

In total, 97.9% (323/330) of results met the accuracy criteria described in ISO 15197:2013 for the user performance evaluation, thus meeting the requirement that 95% of results should be within the accuracy criteria (described in *Appendix 1*).

An overall ease of use rating of 5.5 (out of 6) was obtained when all responses were averaged, indicating that the lay users found the FreeStyle Optium Neo system easy to use – see *Table 1*. The ease of use survey confirmed that the instructions for use and the messages displayed on the meter are adequate, as required by ISO 15197:2013.

Table 1. Ease of Use Rating by 174 Lay Users for FreeStyle Optium Neo System

Statement	Mean Rating*
The test instructions contain sufficient information for me to do a test	5.7
The test instructions are easy to follow	5.6
The meter was easy to learn	5.7
The meter is easy to use	5.6
The meter is easy to hold	5.5
The meter looks attractive	4.7
It was easy to insert the test strip into the meter	5.6
The test strip is easy to use	5.4
It was easy to read the meter display	5.9
Mean over all statements	**5.5**

* The rating scale is 1 to 6 for each statement; 6 is strongly agree & 1 is strongly disagree.

Results – System Accuracy (Trained Operator)

The haematocrit range of the samples in this study was 24 – 56%, and the range of glucose concentrations was 29 – 438 mg/dL (1.6 – 24.3 mmol/L).

Excellent correlation was found between the FreeStyle Optium Neo system and the YSI analyser by regression analysis (r = 0.99, slope = 1.00, intercept = -0.3 mg/dL [-0.02 mmol/L]). Overall the MARD was 5.3% and the mean CV between the paired tests for the 186 samples was 3.4%. Of the 786 test results, 784 (99.7%) were in Zone A (clinically accurate) and 2 (0.3%) were in Zone B (clinically acceptable) of the Consensus Error Grid.

System accuracy analysis for the 3 lots combined showed: 99.1% of results agreed within ±15 mg/dL (0.83 mmol/L) or ±15% (for glucose concentrations ≥100 mg/dL [5.55 mmol/L]) of the reference value – see *Tables 2 to 4*. Results are presented by lot in *Appendix 2*. As required by ISO 15197:2013, each lot showed >95% of results agreed within ±15 mg/dL (0.83 mmol/L) or ±15% of the reference value: 100%, 98.5% & 98.8% for lots A, B and C, respectively.

These results, in combination with the results above confirming that 100% of test strip results were in Zones A & B of the Consensus Error Grid, illustrate that the FreeStyle Optium Neo system meets the accuracy criteria in ISO 15197:2013 (described in *Appendix 1*).

Table 2. System Accuracy Results for Glucose Concentrations <100 mg/dL (5.55 mmol/L)

Accuracy Criteria	Within ± 5 mg/dL (0.28 mmol/L) of reference	Within ± 10 mg/dL (0.56 mmol/L) of reference	Within ± 15 mg/dL (0.83 mmol/L) of reference
Percent (n/n) Within Criteria	**68.2% (105/154)**	**96.8% (149/154)**	**100.0% (154/154)**

Table 3. System Accuracy Results for Glucose Concentrations ≥100 mg/dL (5.55 mmol/L)

Accuracy Criteria	Within ± 5% of reference	Within ± 10% of reference	Within ± 15% of reference
Percent (n/n) Within Criteria	**64.9% (410 / 632)**	**91.9% (581/632)**	**98.9% (625/632)**

Table 4. System Accuracy Results for All Data

Accuracy Criteria	Within ± 5 mg/dL (0.28 mmol/L) or 5% of reference	Within ± 10 mg/dL (0.56 mmol/L) or 10% of reference	Within ± 15 mg/dL (0.83 mmol/L) or 15% of reference
Percent (n/n) Within Criteria	**65.5% (515/786)**	**92.9% (730/786)**	**99.1% (779/786)**

Laboratory Studies

The following studies were performed at Abbott Diabetes Care.

Precision

Materials & Method

Repeatability was evaluated using 10 meters, 3 test strip lots, and 1 venous blood sample with glucose concentrations adjusted to five concentration ranges. 10 measurements were made with each combination of meter, test strip lot and sample. Testing was completed in 1 day.

Intermediate precision was evaluated using 10 meters, 3 test strip lots and 3 levels of control solution, representing hyperglycaemic, euglycaemic and hypoglycaemic conditions. Each sample was tested in duplicate on 3 test strip lots and 10 meters on each of 20 days.

The methods used in the precision studies are based on those outlined in ISO 15197:2013.

Results

Repeatability: Precision was pooled for 300 tests performed across 3 test strip lots using fresh venous blood, at each of 5 glucose concentrations – see *Table 5*. The pooled SD was ≤2.7 mg/dL (0.15 mmol/L) at glucose concentrations <100 mg/dL (5.55 mmol/L) and the pooled CV was ≤3.5% at glucose concentrations ≥100 mg/dL (5.55 mmol/L).

Table 5. Repeatability (adjusted venous samples)

Glucose level		Low	Low-Mid	Mid	Mid-High	High
Mean test strip response	mg/dL	47.3	86.9	145.8	206.4	332.9
	mmol/L	2.6	4.8	8.1	11.5	18.5
Pooled SD	mg/dL	1.9	2.7	4.5	7.3	10.0
	mmol/L	0.10	0.15	0.25	0.41	0.55
Pooled CV, %		4.0	3.1	3.1	3.5	3.0

Intermediate: Precision was pooled for 1200 tests performed across 3 test strip lots over 20 days, at each of 3 glucose concentrations – see *Table 6*. The pooled SD was ≤3.3 mg/dL (0.18 mmol/L) at glucose concentrations <100 mg/dL (5.55 mmol/L) and the pooled CV was 3.1% at glucose concentrations ≥100 mg/dL (5.55mmol/L).

Table 6. Intermediate Precision (quality control solution samples)

Glucose level		Low	Low-Mid	High
Mean test strip response	mg/dL	43.2	91.7	292.5
	mmol/L	2.4	5.1	16.2
Pooled SD	mg/dL	1.9	3.3	9.0
	mmol/L	0.11	0.18	0.50
Pooled CV, %		4.4	3.6	3.1

Haematocrit

Materials & Method

The effect of haematocrit on performance of the FreeStyle Optium Neo system was evaluated using 5 haematocrit levels, 3 glucose concentrations, 3 venous blood samples (from different subjects) and 3 test strip lots.

Each venous blood sample was adjusted to the 5 haematocrit levels (30, 35, 42 (control sample), 50, & 60%) by separating the plasma from the cells, then adding or removing aliquots of plasma in different proportions. The samples at each haematocrit level were divided into 3 portions and the glucose level of each sample was adjusted to the desired concentration.

30 tests (10 tests per strip lot) were performed for each of the 45 samples. Each sample was also tested on the YSI analyser and the results were used to calculate the bias of the meter results from the mean YSI reference value for each sample.

To determine haematocrit effects, the difference between the average bias (from reference value) of each test sample and the average bias (from reference value) of the control sample (42% haematocrit) was determined.

The methods used in the haematocrit study are based on those outlined in ISO 15197:2013.

Results

For each test strip lot, the average difference in bias between test samples and control samples were less than the criteria detailed in ISO 15197:2013 (described in *Appendix 1*), therefore results for each lot have been combined for presentation here (in line with the guidance in ISO 15197:2013) – see *Table 7*. Differences in the haematocrit level of the blood sample affect results by ≤1.2 mg/dL (0.07 mmol/L) at low glucose concentrations and by ≤3.5% at higher glucose concentrations – these were less than the criteria in ISO 15197:2013, which trigger inclusion of the results in the product labelling.

Table 7. Effect of Haematocrit

Mean YSI Reference Value		Mean Difference in Bias from Control (42% Haematocrit)				
mg/dL	mmol/L	Haematocrit	30	35	50	60
45	2.5	mg/dL	-1.2	-0.8	-0.4	-0.8
		mmol/L	-0.07	-0.04	-0.02	-0.04
111	6.2	%	-1.5	-0.7	-2.3	-3.5
400	22.2	%	-2.1	-3.3	-0.8	-1.9

Interference

Materials & Method

30 substances have been evaluated across paired difference (25), dose response (3) and anticoagulant (2) testing:

Paired Difference: 25 substances (including reducing substances, common medications and non-glucose sugars) were tested for interference using venous blood in two glucose concentration ranges (50-100 mg/dL [2.78-5.55 mmol/L] and 250-350 mg/dL [13.88-19.43 mmol/L]), 3 test strip lots and a paired-sample experimental design.

The glucose level of the venous blood was adjusted to the desired concentrations. Paired samples were then spiked with a concentrated solution of the substance (test sample) and an equal volume of the solvent used to dissolve the substance (control sample). This was repeated for each potentially interfering substance. 30 tests were made per sample. The YSI analyser was used to assign glucose reference values to the samples.

For each sample, the bias of the average measured values (test strip results) from the mean YSI reference value was determined. The difference in bias between test and control samples was then calculated for each substance.

Dose Response: An additional 3 substances were tested for interference using venous blood in two glucose concentration ranges (50-100 mg/dL [2.78-5.55 mmol/L] and 250-350 mg/dL [13.88-19.43 mmol/L]), 3 test strip lots and a dose response experimental design.

The glucose level of the venous blood was adjusted to the desired concentrations. For each glucose concentration, the sample was divided into 6 aliquots, 4 test samples & 2 control samples. The test samples were then spiked with different concentrations of the substance and an equal volume of the solvent used to dissolve the substance was added to each of the control samples. This was repeated for the 3 potentially interfering substances. 30 tests were made per sample. The YSI analyser was used to assign glucose reference values to the samples.

A regression model was fit (across lots) between the individual test responses and the interferent concentration. The regression model was used to calculate the interferent concentration at which the effect on performance is considered clinically significant (10% change in the response at the control (zero) concentration).

The methods used in the interference studies are based on those outlined in ISO 15197:2013 and CLSI EP-7A.[6]

Anticoagulants & pH: Potential interfering effects from common anticoagulants (heparin & EDTA, including short fill of tubes) were evaluated by comparing average measured values (test strip results) to the mean YSI reference value and effects of pH were evaluated by comparing difference in bias from reference for control & test pH levels, covering the pH range 7.01 to 7.74.

Results

Paired Difference: The 25 potentially interfering substances undergoing paired difference testing were evaluated at concentrations above the upper limit of therapeutic or normal concentration. Results for each test strip lot have been combined for presentation here – see *Table 8*. Presence of the 25 substances in the blood sample affected results by ≤6 mg/dL (0.36 mmol/L) at low glucose concentrations and by less than 4% at higher glucose concentrations – these were less than the criteria in ISO 15197:2013, which trigger inclusion of the results in the product labelling. Therefore, at the specified test concentrations, none of these substances had an interferent effect on the FreeStyle Optium Neo system.

Dose Response: The 3 potentially interfering substances undergoing dose response testing were evaluated over a range of concentrations, with the maximum test concentration being above the upper limit of therapeutic or normal concentration. The concentration at which each substance was determined to show a clinically significant effect on performance is shown in *Table 9*. The clinically significant concentration was above the therapeutic or normal concentration in each case, therefore these substances were not considered to have an effect on the FreeStyle Optium Neo system. However a limitation will be included in the test strip insert that the product should not be used during a xylose absorption test for malabsorption, where high concentrations of xylose can be present.

Anticoagulant & pH: Presence of lithium heparin and EDTA in the blood sample affected results by ≤6 mg/dL (0.33 mmol/L) at low glucose concentrations and by ≤10% at higher glucose concentrations – these were less than the criteria in ISO 15197:2013, which trigger inclusion of the results in the product labelling. This evaluation included half filling & quarter filling the tubes, in order to evaluate concentrations at 2x and 4x the concentration expected from full tubes.

Blood samples with pH across the range 7.01 to 7.74 affected results by ≤2.2 mg/dL (0.12 mmol/L) at low glucose concentrations and by ≤3.8% at higher glucose concentrations.

Table 8. Paired Difference Interference Testing

Substance	Upper Limit of Therapeutic or Normal Concentration,[6,7] mg/dL (mmol/L)	Test Concentration, mg/dL (mmol/L)	Mean Difference in Bias from Control		
			Mean YSI Reference = 83 mg/dL (4.6 mmol/L)		Mean YSI Reference = 316 mg/dL (17.5 mmol/L)
			mg/dL	mmol/L	%
Acetaminophen (Tylenol, Paracetamol)	3 (0.20)	20 (1.32)	0	0.02	-2
Beta-hydroxybutyrate	<7.6 (0.73)	265 (25.46)	-1	-0.07	-1
Bilirubin (unconjugated)	1.2 (0.02)	20 (0.34)	1	0.05	-2
Cholesterol	<200 (5.18)	503 (13.01)	6	0.36	3
Creatinine	1.3 (0.115)	5 (0.442)	5	0.29	4
Dopamine	0.03 (1.96 µmol/L)	0.10 (6.53 µmol/L)	1	0.07	-1
Ethanol	200 (43.38)	400 (86.77)	2	0.10	-1
Galactose	5.05 (0.28)	15 (0.83)	1	0.04	-1
Gentisic Acid	0.6 (0.039)	1.8 (0.117)	1	0.04	2
Haemoglobin	200 (0.031)	200 (0.031)	1	0.04	-3
Ibuprofen (Montril, Advil)	5 (0.24)	50 (2.42)	0	0.00	1
Icodextrin	460	460	1	0.04	-1
L-Dopa	0.2 (0.010)	0.6 (0.030)	0	-0.01	2
Lactate	20 (2.22)	59 (6.55)	4	0.22	-1
Maltose	-	110 (3.21)	2	0.08	-2
Maltotetraose	-	60 (0.90)	-1	-0.06	-4
Maltotriose	-	120 (2.38)	0	-0.02	-2
Methyl-Dopa (Aldomet)	0.75 (0.036)	1.5 (0.071)	1	0.06	0
Pralidoxime Iodide	205 (7.76)	205 (7.76)	2	0.12	2
Salicylic Acid (from Aspirin)	30 (2.17)	60 (4.34)	3	0.17	-4
Tetracycline	0.5 (0.011)	1.5 (0.034)	-2	-0.10	3
Tolazamide (Tolinase)	2.8 (0.09)	15 (0.48)	2	0.09	3
Tolbutamide (Orinase)	10.8 (0.40)	64 (2.37)	4	0.23	2
Triglycerides	<150 (1.7)	1500 (17)	-1	-0.03	-2
Uric Acid	7.2 (0.43)	24 (1.43)	2	0.10	3

Table 9. Dose Response Interference Testing

Substance	Upper Limit of Therapeutic or Normal Concentration,[6,7] mg/dL (mmol/L)	MaximumTest Concentration, mg/dL (mmol/L)	Clinically Significant Concentration			
			Mean YSI Reference = 87 mg/dL (4.8 mmol/L)		Mean YSI Reference = 308 mg/dL (17.1 mmol/L)	
			mg/dL	mmol/L	mg/dL	mmol/L
Ascorbate (Vitamin C)	1.5 (0.085)	6.0 (0.341)	2.6	0.15	7.9	0.45
Glutathione	0.18 (0.006)*	92.1 (3.00)	22.5	0.73	73.3	2.39
Xylose	50 (3.33)	100 (6.66)	82.4	5.49	374.2	24.9

* Glutathione exists mainly within cells, the extracellular concentration is significantly lower than the intracellular concentration. Since FreeStyle Optium Neo system does not measure intracellular concentrations, the observed plasma glutathione concentration (2 – 6 µmol/L observed across studies[8,9,10,11]) has been used as the normal physiological concentration.

Altitude

Materials & Method

The effect of altitude on the performance of the FreeStyle Optium Neo system was evaluated at 2 altitudes (sea level and 10000 feet; 3048 meters), using 3 venous blood samples (from different subjects), 3 glucose concentrations and 3 test strip lots. 30 tests (10 tests per strip lot) were performed for each of the 18 samples. Each sample was also tested on the YSI analyser and the results were used to calculate the bias of the meter results from the mean YSI value for each sample. To determine altitude effects, the difference between the average bias (from reference) of the testing performed at high altitude and the average bias of the control samples (sea level) was determined.

Results

High altitudes of up to 10000 feet (3048 meters) affect results by <2.3 mg/dL (0.13 mmol/L) at low glucose concentrations and by <3.5% at higher glucose concentrations. This magnitude of change associated with extreme altitudes is clinically acceptable.

Table 10. Effect of Altitude

Altitude	Mean YSI Reference Value, mg/dL (mmol/L)	Difference in Bias from Control (Sea Level)	
Sea Level	49 (2.72)	mg/dL	2.3
10000 ft (3048 m)	41 (2.28)	mmol/L	0.13
Sea Level	110 (6.11)	%	-3.5
10000 ft (3048 m)	104 (5.77)		
Sea Level	391 (21.70)	%	0.1
10000 ft (3048 m)	390 (21.65)		
Average Bias for Glucose <100 mg/dL (5.55 mmol/L), mg/dL (mmol/L)			2.3 (0.13)
Average Bias for Glucose ≥100 mg/dL (5.55 mmol/L), %			-1.8

Discussion

The FreeStyle Optium Neo system has demonstrated excellent performance throughout the evaluations reported here. The clinical, user and laboratory studies illustrate that the system has excellent accuracy and ease of use.

Reliable and Accurate Results for Home Monitoring

Accuracy was verified with capillary blood samples across the measurement range of the system, the haematocrit range of 30 to 60%, at high altitude (1000 feet; 3048 meters), and in the presence of 30 potentially interfering substances.

FreeStyle Optium Neo system delivers accurate results from fingertip capillary samples in testing by trained operators and lay users; >99% of results were in the "clinically accurate" Zone A of the Consensus Error Grid for both user groups. The system accuracy evaluation (performed by trained operators, in line with ISO 15197:2013) showed 99.1% of results agreed within ±15 mg/dL (0.83 mmol/L) or ±15% (for glucose concentrations ≥100 mg/dL [5.55 mmol/L]) of the reference value. Thus the system meets the accuracy criteria introduced in ISO 15197:2013.

FreeStyle Optium Neo system maintains accuracy across the haematocrit range. Extreme haematocrit levels affect the system by ≤1.2 mg/dL (0.07 mmol/L) at low glucose concentrations and by ≤3.5% at higher glucose concentrations, the effects observed were less than the criteria introduced in ISO 15197:2013, which trigger reporting the haematocrit sensitivity in the product labelling.

FreeStyle Optium Neo system minimises the potential for interference. Use of GDH-NAD ensures high specificity of the test to glucose. Consequently, there is no interference from other sugars such as galactose and maltose in dialysis patients that use icodextrin-containing solution for dialysis. The system should not be used during xylose absorption testing. Use of a low potential in the electrochemical reaction also minimises interference from reducing substances commonly found in the blood, such as acetaminophen (paracetamol) and uric acid. Each of the substances tested had no clinically significant effect on FreeStyle Optium Neo system results, the effects observed were less than the criteria introduced in ISO 15197:2013, which trigger reporting the substance as an interferent in the product labelling.

Convenience and Ease of Use

The FreeStyle Optium Neo system is designed to be easy and convenient to use for frequent monitoring of blood glucose:

- **Rated easy to use by first time users.** The overall mean rating by 174 lay users was 5.5 (on a scale of 1 to 6).
- **Requires no calibration or coding by the user.**
- **Has a fast test time & requires a small blood sample.** The system takes only 5 seconds per test and requires a small sample (0.6 µL minimum), which facilitates alternate site testing.

- **Allows easy application of blood.** The user can apply blood to the top or the end of the test strip and the blood is automatically drawn into the reaction site. The design provides equal convenience to left-handed and right-handed users and the features make testing easier for caregivers or users with limited dexterity.
- **Autostarts** when the sample is detected.
- **Allows re-application of sample.** If the test does not start after the first application of blood, a second sample of blood can be applied to the same test strip within 5 seconds.

Reduced Use Error

Use error is a major concern in home glucose monitoring. The FreeStyle Optium Neo system is designed to reduce use error in everyday testing conditions:

- **Reduce risk associated with underfilling test strips.** Erroneous results ranging from 85% lower to 39% higher have been reported when a small drop of blood is used with some blood glucose monitoring systems.[12,13,14,15,16] The sample detection (fill trigger) electrode in test strips used with the FreeStyle Optium Neo system ensures that the test only starts when sufficient sample is applied, minimising the potential for error from 'short' sampling. Furthermore, the fill confirmation window (via the semi-opaque tape layer) allows the user to confirm sufficient sample is applied before they withdraw their finger from the test strip.
- **Individually foil wrapped.** Exposure of test strips in a vial to air and moisture is common, for example if vials are not capped promptly and tightly after each opening. Test strips exposed to air for as little as 2 hours have been shown to cause a -26% bias.[17] Each FreeStyle Optium test strip is individually wrapped in easy to open foil, to protect it against air, moisture and other contaminants.

Conclusions

In conclusion, the studies described in this paper show that the FreeStyle Optium Neo Blood Glucose and Ketone Monitoring System delivers accurate, reliable glucose results whilst providing safeguards to ensure the integrity of the testing process. Specifically, the clinical studies demonstrated the accuracy of the FreeStyle Optium Neo system for capillary self-testing – accuracy of the system in the hands of the lay user and trained operators meets the accuracy criteria introduced in ISO 15197:2013. In user performance testing, the system had a high acceptance and ease of use rating among first-time users. Laboratory studies showed that the test strip performs well in the presence of interfering substances and across the claimed haematocrit range, the magnitude of the effect of these influence quantities was less than the criteria introduced in ISO 15197:2013, which trigger inclusion in the product labelling. Combined with features that can minimise short sampling and test strip contamination, the short test time and no requirement for coding or calibration by the user, these results show that the FreeStyle Optium Neo system is uniquely designed to provide accurate and reliable results in self-testing by people with diabetes.

Appendix 1 – Performance Requirements in ISO 15197:2013

User Performance Accuracy Evaluation (8.2)

95% of the individual glucose measured values shall fall within ±15 mg/dL (0.83 mmol/L) of the measured values of the manufacturer's measurement procedure at glucose concentrations <100 mg/dL (5.55 mmol/L) and within ±15% at glucose concentrations ≥100 mg/dL (5.55 mmol/L).

System Accuracy (6.3.3)

System accuracy criteria apply to studies performed by trained operators. The BGMS shall meet both of the following minimum criteria for acceptable system accuracy:

a. 95% of the measured glucose values shall fall within either ±15 mg/dL (0.83 mmol/L) of the average measured values of the reference measurement procedure at glucose concentrations <100 mg/dL (5.55 mmol/L) or within ±15% at glucose concentrations ≥100 mg/dL (5.55 mmol/L).

b. 99% of individual glucose measured values shall fall within Zones A and B of the Consensus Error Grid for Type 1 diabetes.[5]

Criteria (a) shall apply to each test strip lot individually. The measured values from each lot shall be analysed and reported separately.

Criteria (b) shall be applied to the 3 test strip lots taken together. All measured values from the 3 lots shall be combined before analysis and reporting.

Haematocrit (Packed Cell Volume, 6.4.3.2)

Packed cell volume effects shall be described in the instructions for use if they meet either of the following performance criteria:

- For glucose concentrations <100 mg/dL (5.55 mmol/L), the difference between the average measured value at each packed cell volume level and the average measured value at the mid-level packed cell volume exceeds 10 mg/dL (0.55 mmol/L).
- For glucose concentrations ≥100 mg/dL (5.55 mmol/L), the difference between the average measured value at each packed cell volume level and the average measured value at the mid-level packed cell volume exceeds 10%.

Interference (6.4.4.2)

The interference effects shall be described in the instructions for use if they meet either of the following performance criteria:

- For glucose concentrations <100 mg/dL (5.55 mmol/L), the average difference between the test sample and the control sample exceeds 10 mg/dL (0.55 mmol/L).
- For glucose concentrations ≥100 mg/dL (5.55 mmol/L), the average difference between the test sample and the control sample exceeds 10%.

Appendix 2 – System Accuracy Analysis by Test Strip Lot

(Trained operator results, in line with ISO 15197:2013)

Table 11. System Accuracy Results for Glucose Concentrations <100 mg/dL (5.55 mmol/L)

Test Strip Lot	Within ± 5 mg/dL (0.28 mmol/L)	Within ± 10 mg/dL (0.56 mmol/L)	Within ± 15 mg/dL (0.83 mmol/L)
A	44 / 58 (75.9%)	56 / 58 (96.6%)	58 / 58 (100.0%)
B	30 / 46 (65.2%)	43 / 46 (93.5%)	46 / 46 (100.0%)
C	31 / 50 (62.0%)	50 / 50 (100.0%)	50 / 50 (100.0%)
Overall	105 / 154 (68.2%)	149 / 154 (96.8%)	154 / 154 (100.0%)

Table 12. System Accuracy Results for Glucose Concentrations ≥100 mg/dL (5.55 mmol/L)

Test Strip Lot	Within ± 5%	Within ± 10%	Within ± 15%
A	139 / 204 (68.1%)	189 / 204 (92.6%)	204 / 204 (100.0%)
B	131 / 218 (60.1%)	197 / 218 (90.4%)	214 / 218 (98.2%)
C	140 / 210 (66.7%)	195 / 210 (92.9%)	207 / 210 (98.6%)
Overall	410 / 632 (64.9%)	581 / 632 (91.9%)	625 / 632 (98.9%)

Table 13. System Accuracy Results for All Data

Test Strip Lot	Within ± 5 mg/dL (0.28 mmol/L) or 5%	Within ± 10 mg/dL (0.56 mmol/L) or 10%	Within ± 15 mg/dL (0.83 mmol/L) or 15%
A	183 / 262 (69.8%)	245 / 262 (93.5%)	262 / 262 (100.0%)
B	161 / 264 (61.0%)	240 / 264 (90.9%)	260 / 264 (98.5%)
C	171 / 260 (65.8%)	245 / 260 (94.2%)	257 / 260 (98.8%)
Overall	515 / 786 (65.5%)	730 / 786 (92.9%)	779 / 786 (99.1%)

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