FREESTYLE™

A meter designed for glucose self-measurement
Manufactured by Abbott Laboratories

Report from an evaluation
organised by

SKUP

The evaluation was ordered by Abbott Norge AS

SKUP/2005/51*

SKUP in Norway, NOKLUS, Division of General Practice, University of Bergen, 5009 Bergen, www.SKUP.nu

Summary

Background
FreeStyle is a meter designed for glucose self-measurements by diabetic patients. The meter is produced and supplied by Abbott. FreeStyle was launched onto the Norwegian market in 2001. An evaluation of FreeStyle was done by SKUP in 2002 (www.skup.nu, SKUP 2002/21).

In order to give reimbursement for the test strips, The National Social Insurance Office (*Rikstrygdeverket*) in Norway has instructed Abbott to carry out a supplementary evaluation that includes the quality of the system of finger measurements done by diabetics. The supplementary evaluation of FreeStyle is done under the direction of SKUP during the autumn of 2005.

The aim of the evaluation
The aim of the evaluation of FreeStyle is to

- reflect the analytical quality of finger measurements done by the users (diabetic patients)
- reflect the analytical quality of finger measurements under standardised and optimal conditions (performed by biomedical laboratory scientist)

Materials and methods
23 diabetic patients took part in the supplementary evaluation. All the diabetics participated in the evaluation of FreeStyle in 2002. In the evaluation in 2002 they were trained in how to use the meter. In this supplementary evaluation the diabetics received FreeStyle by post and no new training was given. After approximately one week they came for a consultation. The diabetics did a finger prick and performed two measurements on the meter. The biomedical laboratory scientist also took capillary samples of the diabetic patients and measured twice at FreeStyle. In addition, two capillary samples were taken to a designated comparison method. One lot of test strips was used in the evaluation.

Results

- FreeStyle shows acceptable precision. The CV is ≤ 5 % both under standardised and optimal measuring conditions and when the measurements are performed by diabetic patients.
- The agreement with a designated comparison method is good. Quality goals set in ISO 15197 are achieved when measurements are done in finger by diabetic patients. 100 % of these results are within the quality goals. The quality goals set in ISO 15197 are also achieved under standardised and optimal measuring conditions.

Conclusion
Glucose measurements done in finger on FreeStyle have acceptable precision. The measurements performed by the diabetic patients and by a biomediacal laboratory scientist are within the quality goals set in ISO-guide 15197.

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Attachments with raw data are included only in the copy to Abbott.

1. The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, SKUP, is a cooperative venture by Norway, Sweden and Denmark. SKUP was established in the autumn of 1997 at the initiative of professionals and health authorities in the three countries. SKUP is led by a Scandinavian expert group. The secretariat is located at NOKLUS Centre in Bergen, Norway.

The goal of SKUP is to produce objective and independent information concerning the quality and user-friendliness of laboratory equipment for physicians' offices outside the hospital. This information is generated by organizing SKUP's own evaluation program.

The SKUP evaluation is standardised according to SKUP's general evaluation guidelines. The evaluation follows a protocol based on these guidelines, but the protocol is always adjusted to the actual evaluation in cooperation with the supplier. The SKUP evaluation consists of two comparable parts. One part of the evaluation is done under standardised and optimal measuring conditions and the other part is performed by the users the equipment is produced for. Primarily, SKUP evaluates equipment intended for the primary health care, but SKUP can also offer evaluations of equipment for self monitoring blood glucose (SMBG). The evaluations of SMBG are conducted under standardised and optimal conditions and among diabetic patients.

SKUP personnel are financed with funds from their respective countries, while the actual testing is funded by the equipment suppliers. For suppliers this offers an opportunity to have their equipment subjected to standardised testing all over Scandinavia. For consumers it means easy access to objective information on equipment, and health care authorities will be able to gain an overview of the equipment (and its quality) available on the market at any given time.

SKUP distributes information about evaluated equipment to physicians' offices, laboratory medical councils, laboratory advisors and health political authorities. The evaluation reports are presented at www.skup.nu.

A unique evaluation code number is assigned to every SKUP evaluation report. The code is composed of the name SKUP, and the year and number of the evaluation. This applies for all evaluations following the complete SKUP standard evaluation procedure. Pre marketing evaluations, evaluations without the user's contribution, supplementary evaluations and special evaluations on request from the producer/supplier are in addition marked with a star in connection to the evaluation number. If the company makes use of SKUP's name in the marketing of an instrument, they have to refer to www.skup.nu and the actual evaluation number at the same time. If required, the company can get access to a SKUP logo where this information is an integral part.

2. Background for the evaluation

SKUP carried out a user evaluation of FreeStyle in 2002. The report from this evaluation, SKUP/2002/21, is found at www.skup.nu.
The FreeStyle monitor is an electrochemical sensor capable of measuring capillary blood samples from different alternate test sites as the forearm, the upper arm, the thigh or calf, and from the fleshy parts of the hand. When FreeStyle was introduced to the Norwegian marked in 2001, alternate site testing (AST) was a relative new possibility for the diabetics. In accordance with the request from the supplier, the evaluation of FreeStyle in 2002 was based on the possibility for AST. Therefore, all the diabetics' self measurements were done at the forearm. Measurements from the finger were only part of the evaluation done under standardised and optimal measuring conditions (explained in chapter 5.4.4).
Glucose results from the finger and AST can differ due to physiological differences of the capillary bed. The discrepancies are most distinctive during rapid blood glucose changes. The differences between finger and AST glucose results brought some interpretation problems in the evaluation in 2002. The finger results under standardised and optimal measuring conditions fulfilled the ISO quality goals. In consequence, as forearm results differ from finger results, the diabetics' forearm results did not fulfil the quality goals. As a result of this, it was not possible to confirm the analytical quality of the diabetics' measurements.
In order to give reimbursement for the FreeStyle test strips, the National Social Office (Rikstrygdeverket) in Norway has instructed Abbott to carry out a supplementary evaluation that includes the analytical quality of the system from finger measurements done by diabetics. It is clarified that results from approximately 20 diabetics will be sufficient. The limited amount of results in this supplementary evaluation must always be seen in association with the results from the main evaluation in 2002.

3. Planning of the evaluation

Ingrid E. Stiff Aamlid from Abbott Norge AS, applied to SKUP in the spring of 2005 for this supplementary evaluation of the glucose meter FreeStyle. In June 2005 SKUP gave a written offer, and the protocol for the supplementary evaluation of FreeStyle was accepted by Abbott in September 2005. A contract was set up between Abbott Norge AS and SKUP in October 2005.

SKUP evaluations are made according to guidelines in the book "*Evaluation of analytical instruments. A guide particularly designed for evaluations of instruments in primary health care*"[1]. The evaluation of a self-monitoring blood glucose device follows the guidelines in the book, but the evaluation in primary health care is replaced by a user-evaluation conducted among diabetics, based on the model by the NOKLUS-project "*Diabetes-Self-measurements*" [2]
The report from the evaluation of FreeStyle in 2001/2002 fulfils these guidelines. The supplementary evaluation comprises the following studies of measurements done in fingers:

- An examination of analytical quality under standardised and optimal conditions done by a biomedical laboratory scientist
- An examination of analytical quality among 23 diabetics
- An examination of agreement between FreeStyle and a designated comparison method

SKUP carried out the supplementary evaluation of FreeStyle blood glucose meter system during the autumn of 2005. The blood sampling of the diabetics and the measurements on FreeStyle under standardised and optimal conditions were done by Åse Hirsch-Nilsen, biomedical laboratory scientist, SKUP/NOKLUS Centre. Wenche Eilifsen Hauge , biomedical laboratory scientist, was given the responsibility for the practical work with the comparison method at the laboratory at Haraldsplass Diaconal Hospital (HDH). The statistical calculations and the report writing are done by Åse Hirsch-Nilsen, SKUP/NOKLUS Centre.

4. Analytical quality specifications

There are different criteria for setting quality specifications for analytical methods. Ideally the quality goals should be set according to the medical demands the method has to meet. For glucose it is natural that the quality specification is set according to whether the analysis is used for diagnostic purpose or for monitoring diabetes. FreeStyle is designed for monitoring blood glucose, and the quality goals must be set according to this.

Precision
For glucose meters designed for monitoring blood glucose one should point out the need of a method with good precision [3]. According to American Diabetes Assosiation (ADA) the imprecision of new glucose devices must be less than 5 % [4]. Other authors also recommend an imprecision of 5 % or less [5].

Accuracy
According to ADA the total error for meters designed for self monitoring and point of care testing of glucose should not exceed 10 % in the range 1,67 – 22,2 mmol/L. The quality goal from ADA must be seen as an optimal goal for the analytical quality of these meters.
The quality goal for the total error of FreeStyle is found in ISO 15197, In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus [6]. The ISO-guide is an international protocol for evaluating meters designed for glucose monitoring systems.

ISO 15197 gives the following minimum acceptable accuracy requirement:

Ninety-five percent (95 %) of the individual glucose results shall fall within ± 0,83 mmol/L of the results of the comparison method at glucose concentrations < 4,2 mmol/L and within ± 20 % at glucose concentrations ≥ 4,2 mmol/L.

This is a quality goal for measurements by trained laboratory staff. Ideally, the same quality requirement should apply for measurements by the diabetics. Previous investigations under the direction of the NOKLUS-project ”Diabetes-Self-measurements” [5, 7], and results from evaluations under the direction of SKUP, have showed that few of the self-monitoring glucose meters that were tested met the ISO-requirements. The results by the diabetics therefore have to be discussed towards a *modified* goal suggested by NOKLUS, with a total error of 25 %. This modified goal has wide, and not ideal, limits. The modified requirements for diabetics will be tightened up over time as the meters improve due to technological development.

Quality demands, adjusted to the diabetics self-measurements:

Ninety-five percent (95 %) of the individual glucose results shall fall within ± 1,0 mmol/L of the results of the comparison method at glucose concentrations < 4,2 mmol/L and within ± 25 % at glucose concentrations ≥ 4,2 mmol/L.

5. Materials and methods

5.1. Statistical terms and expressions

5.1.1. Precision

The common used terms within-series imprecision and between-series imprecision are often misinterpreted. Especially the terms between-series and between-day imprecision are often not precisely defined. In this report, the terms are replaced by the precisely defined terms *repeatability and reproducibility*. Repeatability is the agreement between the results of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series). Reproducibility is the agreement between the results of discontinuous measurements of the same component carried out under changing measuring conditions over time. The reproducibility includes the repeatability. The two terms are measured as imprecision and are expressed by means of the standard deviation (SD) or coefficient of variation (CV). Precision is descriptive in general terms (good, poor), whereas imprecision is an estimate, reported in the same unit as the analytical result (SD) or in % (CV). The imprecision will be summarised in tables.

5.1.2. Accuracy

Accuracy is the closeness of agreement between the result of one measurement and the true value. Inaccuracy is a measure of a single measurements deviation from a true value, and implies a combination of random and systematic error (analytical imprecision and bias). Inaccuracy, as defined by a single measurement, is not sufficient to distinguish between random and systematic errors in the measuring system. Inaccuracy can be expressed as total error. The inaccuracy will be illustrated by difference plots with quality goals for the total error shown as deviation limits in percent.

5.1.3. Trueness

Trueness is the agreement between an average value obtained from a large number of measuring results and a true value. Trueness is measured as bias (systematic errors). Trueness is descriptive in general terms (good, poor), whereas bias is the estimate, reported in the same unit as the analytical result or in %. The bias is not measured in this supplementary evaluation because of few data (n=23).

5.2. FreeStyle

FreeStyle is a blood glucose monitoring system based on electrochemical technology (coulometri). The system consist of a meter and dry reagent test strips designed for capillary blood glucose testing by people with diabetes or by health care professionals. The system is calibrated to report plasma values of glucose. The system requires calibration by the user. Code numbers are used to calibrate meters with the test strips to ensure proper operation of the system. The user has to make sure that the code number displayed by the meter when the meter is activated matches the code number printed on the test strip package. The test strip chemistry uses a pyrroloquinoline quinone-glucose dehydrogenase (PQQ-GDH). PQQ serves as a cofactor and this enzyme system offers the advantages to reduced sensitivity to oxygen compared to glucose oxidase based systems.

The test strips are packaged in a plastic bottle with flip-top closure and desiccant. The system requires a blood volume of 0,3 µL and provides a result in approximately 7 seconds. The meter has the capability of storing 250 results in the memory. When analysing a FreeStyle Control Solution, the meter does not detect that it is a control solution and the user has to mark the result as a control. FreeStyle is cleared for multiple site testing. The meter can be used on less sensitive testing sites like the forearm, upper arm, palm, calf or thigh. Abbott recommends consulting Healthcare Professional if use of multiple sampling sites. The FreeStyle adjustable lancing device is used to form a drop of blood on the fingertip. Abbott has available a software to download the meter's information to a computer through the meter data port. Technical data from the manufacturer is shown in table 1.

Table 1. Technical data from the manufacturer

TECHNICAL DATA FOR FREESTYLE	
Ambient temperature	5 – 40 °C
Sample volume	0,3 µL
Measuring time	Approximately 7 seconds
Measuring range	1,1 – 27,8 mmol / L
Hematokrit	15 – 65 %
Memory	250 tests
Power supply	1 × 3,0 V Lithium nr 2032 battery
Operating time	Approximately 1000 tests
Dimensions	W= 51 mm, H= 97 mm, D= 25 mm
Weight	58 g (included the battery)

5.2.1. Product information, FreeStyle

FreeStyle blood glucose meter system:
Manufactured by: Abbott Laboratories.

Suppliers of FreeStyle in Scandinavian countries:

Sweden:	Denmark	Finland	Norway:
Abbott Scandinavia AB	Abbott Laboratories AS	Abbott Oy	Abbott Norge AS
Gårdsvägen 8, Solna	Abbott Diabetes Care	Abbott Diabetes Care	Abbott Diabetes Care
Box 509	Smakkedalen 6	Pihatorma 1A	PB 1
16929 Solna	2820 Gentofte	02240 Espoo	1330 Fornebu
Sweden	Denmark	Finland	Norway
Phone: 020-1901111	Phone: 45 80815354	Phone: 45 80815354	Phone: 815 59 920

During this user-evaluation 24 FreeStyle blood glucose meters were used.
Attachment 1 gives serial numbers for the 24 meters.

FreeStyle glucose test strips:
Lot-no.0517206 Expiry 2007-06

FreeStyle Control Solution:
Lot-no. 4F3L02 (high) Expiry 2006-09

FreeStyle lancetpen with 26G lancets

5.3. Designated comparison method

Definition
A designated comparison method is a fully specified method, which, in the absence of a reference method, serves at the common basis for the comparison of a field method.

Verifying of trueness
The results from SMBG-devices must be compared with a recognized comparison method. The comparison method should be a plasma method, hexokinase by preference. The method has to show traceability equivalent to that of an internationally accepted reference material, such as the standards supplied by the National Institute of Standards & Technology, NIST. The NIST-standard SRM 965a with four levels of glucose concentrations was used in this evaluation. In addition, freshly frozen, human serum controls from NOKLUS with glucose concentrations at two levels were analysed. The NOKLUS-controls have target values determined with an isotope-dilution gas chromatography/mass spectrometry method at a Reference laboratory in Belgium; Laboratory for Analytical Chemistry, University of Gent, Belgium [8]. The results are summarized in chapter 7.1.2.

The designated comparison method in this evaluation
In this evaluation, the routine method for quantitative determination of glucose in human serum, plasma (lithium heparin) and urine at the Laboratory at Haraldsplass Diaconal Hospital was used as the designated comparison method. The method will be called *the comparison method* in this report. The comparison method is a photometric enzymatic method based on the method by Slein, utilising hexokinase and glucose-6-phosphate dehydrogenase enzymes. The method is implemented on the Advia 1650 Chemistry System from Bayer, with reagents and calibrators from Bayer. The Advia 1650 Chemistry System Glucose Hexokinase II method is a two-component reagent. Sample is added to Reagent 1, which contains buffer, ATP and NAD. Absorbance readings of the sample in Reagent 1 are used to correct for interfering substances in the sample. Reagent 2 is added, which initiates the conversion of glucose and the development of an absorbance at 340 nm. The difference between the absorbance in Reagent 1 and Reagent 2 is proportional to the glucose concentration. The measuring principle in the Advia 1650 is as follows: Glucose is phosphorylated by ATP in the presence of hexokinase. The glucose-6-phosphate that forms is oxidised in the presence of glucose-6-phosphate dehydrogenate causing the reduction of NAD to NADH. The absorbance of NADH is measured as an endpoint reaction at 340 nm.

Internal quality assurance of the Advia 1650 comparison method during the evaluation period
The Autonorm Human Liquid Control Solutions at two levels from Sero AS were part of the measuring series for this evaluation. The controls were measured as the first and the last samples in all the series.

5.3.1. Product information, comparison method

Designated comparison method Advia 1650
Manufactured by: Bayer AS
Serial no. CA 175524-196

Reagents
Bayer Glucose Hexokinase method II (B01-4597-01)
Lot-no. 42073

Calibrator
Chemistry Cal Bayer
Lot-no. 179747 Expiry 2005-10 Reference value = 13,5 mmol/L

Internal control
Seronorm Autonorm Human Liquid 1 and 2, Sero AS
Liquid 1: Value = 5,2 ± 0,36 mmol/L Lot-no. NO3588 Expiry 2006-01
Liquid 2: Value = 15,0 ± 1,05 mmol/L Lot-no. MI4298 Expiry 2006-07

NOKLUS control
(ID-GCMS method; reference value from Laboratory for Analytical Chemistry, University of Gent, Belgium)
Level 1: Value = 3,20 ± 0,010 mmol/L
Level 2: Value = 7,78 ± 0,026 mmol/L

NIST standards
Standard Reference Material® 965a, National Institute of Standards & Technology
Level 1: Value = 1,918 ± 0,020 mmol/L Expiry 2008-12-31
Level 2: Value = 4,357 ± 0,048 mmol/L Expiry 2008-12-31
Level 3: Value = 6,777 ± 0,073 mmol/L Expiry 2008-12-31
Level 4: Value = 16,24 ± 0,19 mmol/L Expiry 2008-12-31

Tubes used for sampling for the designated comparison method
Microvette CB 300 LH (litium-heparin) manufactured by Sarstedt AS
Lot-no. 5070201 Expiry 2008-01

Blood sampling device
Accu-Chek SoftClix Pro

Accu-Chek SoftClix Pro lancets:
Lot-no. W10 35D3 Expiry 2007-12-31

Centrifuge used for samples for the designated comparison method:
Eppendorf 5415D

5.4. Evaluation procedure

5.4.1. Model for the evaluation

The practical work with the evaluation was carried out during 2 weeks in autumn 2005 (from week number 39 to week number 40) at NOKLUS Centre, Bergen in Norway. The practical work was done by biomedical laboratory scientist Åse Hirsch-Nilsen.

The supplemantary evaluation consisted of two parallel evaluations. One part of the evaluation was done by the biomedical laboratory scientist under standardised and optimal conditions. This part of the evaluation is done by laboratory educated personnel, completely according to the protocol and user manual after having received thoroughly training. All possibilities for disturbance of, and interferences with, the measurements were tried kept at a minimum. The evaluation under standardised and optimal conditions documents the quality of the system under best possible conditions. The other part of the evaluation was done by diabetics. 23 diabetics participated in the supplementary evaluation, in order to determine the analytical quality of samples from finger done with FreeStyle by the users. The diabetics received the blood glucose meter and instructions by post. The model for the supplementary evaluation is shown in figure 1.

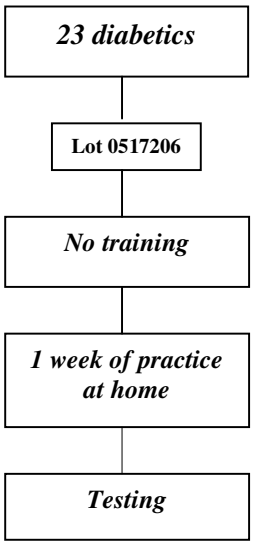

Figure 1. Model for the supplementary evaluation

5.4.2. Recruiting of the diabetics

The FreeStyle glucose meter was tested in use by 23 diabetics. The group of diabetics were recruited from the evaluation of FreeStyle done in 2002. In the evaluation in 2002 they were trained in how to use the meter. Today, a few of the diabetics still use FreeStyle. The group of diabetics was representative for diabetics who carry out self-monitoring of blood glucose (SMBG). The group included diabetics from across a range of self-monitoring frequencies, i.e. diabetics who performed self-monitoring often (one or more times a day) and those who performed self-monitoring less frequently (once a week).
Patient characteristics of the group are shown in table 2.

Table 2. Characteristics of diabetic patients included (n=23).

		Diabetic patients
Total		23
Sex	Men	11
	Women	12
Age, median (range)		55 (15-74)
Diabetes	Type 1	11
	Type 2	12
Treatment	Insulin	14
	Tablets	6
	Insulin and tablets	2
	Diet	1
Frequency of SMBG	Less than weekly	1
	1 -3 per week	3
	4 – 6 per week	0
	7 – 10 per week	1
	> 10 per week	18

The SMBG-devices that the diabetic patients use regularly: Accu-Chek (1), Accu-Chek Compact/Compact Plus (5), Accu-Chek Comfort (1), Ascensia Contour (3), Ascensia DEX/DEX2 (3), Ascensia Elite (2), OneTouch Ultra (2), InDuo (1), GlucoTouch (1), MediSense Precision QID (1), FreeStyle (1) and FreeStyle Mini (2).
Some of the diabetic patients used more than one SMBG-device at home, but only one device is registered here.

5.4.3. The consultation at NOKLUS Centre

23 diabetics received the FreeStyle device by post, along with test strips, lancet pen, lancets, user manual and an instruction letter with explanations regarding what to do with the FreeStyle device during the period at home. No training was given. The diabetics used the meter over a week period at home. After this period, they attended a consultation at NOKLUS Centre.

Blood sampling
After the week practice period at home, the 23 diabetics were called for, one by one, to a consultation. Each diabetic brought their assigned FreeStyle meter. They got test strips from the biomedical laboratory scientist at NOKLUS Centre. They made duplicate blood glucose tests on FreeStyle. These results were registered for the supplementary evaluation.

Internal quality control
The diabetics are not familiar with control solutions for self-measurements. Therefore they were not instructed to use control solution on FreeStyle in the evaluation. To document correct functioning on the FreeStyle meters used by the diabetics during the test period, the biomedical laboratory scientist in charge of the practical work controlled the meters when the diabetics were at the consultation.

5.4.4. Evaluation under standardised and optimal conditions

The biomedical laboratory scientist used one FreeStyle blood glucose meter for the evaluation (meter "A"), and only one lot of test strips was used.

Blood sampling
Meter "A" was checked by means of the manufacturer's control solution every day it was used. The blood sampling and analysis were done in the following order:

1. The biomedical laboratory scientist took a sample for the comparison method
2. The diabetic finger pricked themselves and took duplicate samples for their assigned meter
3. The biomedical laboratory scientist took samples and analysed twice on meter "A"
4. The biomedical scientist took a new sample for the comparison method
5. The biomedical laboratory scientist measured internal quality control at the diabetic's meter

All sampling was done from the fingers, and the duration of the sampling did not exceed 10 minutes. The blood samples for the comparison method were always taken first and last in accordance with ISO 15197.

The biomedical laboratory scientist registered whether the diabetic needed help to set the right calibration code in the blood glucose meter before sampling, if they used correct cleaning, drying, and skin puncture procedure, applied the blood sample correctly to the test strip, and otherwise followed the manufacturer's instructions for performing a glucose meter test. 8 of 23 diabetics needed guidance to set the right calibration code, and one diabetic was corrected trying to fill the test strip with blood from both side of the strip.

Handling of the samples for the comparison method
The samples for the comparison method were capillary taken using a Microvette Li-heparin tube from Sarstedt. The samples were centrifuged immediately for three minutes at 10 000 g, and plasma was separated into sample vials for Advia 1650. The samples were frozen directly as the plasma was separated and the plasma was stored at minus 80 °C.

Analysing the samples for the comparison method
The samples were analysed at Advia 1650. The samples were thawed at NOKLUS Centre just before they were analysed. The first and the second sample for the comparison method, taken at the start and at the end of each blood sampling, reflect the stability of the glucose concentration during the sampling time. The difference between the first and the second comparative reading was not allowed to be more than 4 % or 0,22 mmol/L (per ISO 15197 Section 7.3.2.). If the difference between any paired results exceeded these limits, the samples were re-analysed. If the result from the re-run confirmed the difference, the difference was looked upon as a real difference in the glucose concentration in the two samples. Deviations > 10 % were regarded as not acceptable and such results would be excluded. As a consequence of this, the matching FreeStyle results were excluded for accuracy calculations. Differences between 4 and 10 % are included in the calculations. In spite of this deviation on the comparison method, these results still fulfil the quality goals. If the deviation between the two results was not confirmed by the re-run, the result from the re-run was used as the accepted result. Recommended minimum volume for analysis of glucose on Advia 1650 in this supplementary evaluation was 120 µL plasma.

5.4.5. Evaluation of analytical quality

The following sets of data give the basis for the evaluation of the analytical quality:

1. Results from 23 diabetics who had not participated in a new training programme, but who had practised using FreeStyle at home for one week
2. Results from 23 measurements under standardised and optimal conditions
3. Results from 23 measurements from the comparison method.

The results from the diabetics and the biomedical laboratory scientist were compared (group 1 and 2). All the diabetic measurements were evaluated against the results achieved under standardised and optimal conditions.

6. Statistical calculations

6.1. Number of samples

All the diabetics completed the supplementary evaluation. They met for one consultation where the blood samples were taken. This means that the total number of samples is 23 x 2 (duplicates) x 3 (meter A, diabetic's meter, the comparison method) = 138 samples. The results will not be divided into groups according to different glucose concentration levels, because the number of data (n=23) are small.

6.2. Statistical outliers

All results are checked for outliers according to Burnett [9], with repeated truncations. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is often set to 5 %, so also in this evaluation. No outliers were found in this supplementary study.

6.3. Missing or excluded results

One result is excluded:

- ID number 160 had a difference > 10 % between the paired results on the comparison method. The difference was confirmed by a re-run. As a consequence of this, the results from ID 160 are excluded when FreeStyle is compared with the comparison method (accuracy), but included in the calculations regarding the imprecision at FreeStyle.

6.4. Calculation of imprecision based on duplicate results

Two capillary samples were taken of each diabetic patient to meter "A", the diabetic's meter and to the comparison method. The imprecision was calculated by use of paired measurements, based on the following formula:

$$SD = \sqrt{\frac{\sum d^2}{2n}}$$, d= difference between two paired measurements, n = number of differences

The assumption for using this formula is that there must be no systematic difference between the 1st and the 2nd measurement. Table 3 shows that there is no significant difference in glucose concentration between the paired measurements on FreeStyle in this evaluation.

Table 3. No systematic differences between the 1st and the 2nd measurement. T-test for paired values.

		Glucose level mmol/L	Mean 1st measurement mmol/L	Mean 2nd measurement mmol/L	Mean difference 2nd – 1st measurement mmol/L	P	n
FreeStyle	Meter A	3,4-15,6	8,5	8,6	0,1	0,248	23

6.5. Calculation of accuracy

To evaluate the accuracy of the results at FreeStyle, the agreement between FreeStyle and the comparison method is illustrated in difference plots. In the plots the x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at FreeStyle and the mean value of the duplicate results at the comparison method.

7. Results and discussion

7.1. Precision and trueness of the designated comparison method

7.1.1. The precision of the comparison method

The repeatability of the comparison method is shown in table 4 and table 5. The results are obtained with the SRM 965a standards supplied by NIST, and freshly frozen, human serum controls from NOKLUS.

The reproducibility of the comparison method is not calculated because all the reference samples were analysed at one day. From earlier evaluations Advia1650 has shown a reproducibility < 1,0 CV%.

Discussion
The precision of the comparison method is good. The repeatability is ≤ 0,5 CV%.

7.1.2. The trueness of the comparison method

In order to demonstrate the trueness of the comparison method, the SRM 965a was analysed at the comparison method. SRM 965a consists of ampoules with human serum with certified concentrations and uncertainties for glucose at four concentrations. The SRM 965a materials cover a glucose concentration range from 1,9 to 16,2 mmol/L. The agreement between the comparison method and the NIST-standards is shown in table 4.

Table 4. The comparison method – Standard Reference Material (SRM 965a) measured on the comparison method during the evaluation period

SRM 965a	Date	Target value mmol/L (uncertainty)	Mean value glucose (mmol/L)	n	CV % (95 % CI)	% deviation from target value
Level 1	7.10.2005	1,918 (1,898-1,938)	1,936	5	1,0 (0,6-2,8)	0,9
Level 2	7.10.2005	4,357 (4,309-4,405)	4,424	5	0,5 (0,3-1,4)	1,5
Level 3	7.10.2005	6,777 (6,704-6,850)	6,898	5	0,4 (0,2-1,1)	1,8
Level 4	7.10.2005	16,24 (16,05-16,43)	16,546	5	0,2 (0,1-0,6)	1,9

Table 4 reveals that glucose results at Advia 1650 are approximately 1,0-2,0 % higher than the target values from NIST. Even though the obtained results are only just outside the given uncertainty limits for the Reference Material, it was decided that all results from Advia should be adjusted according to the findings presented in the table above. The findings and the degree of adjustment are in accordance with four user-evaluations carried out by SKUP during the spring and summer of 2005.The adjustment was done by means of the following regression equation ($R^2 = 1,0$):

$y = 0,9803x + 0,0187$

From now on in this report, whenever any result from Advia is presented, the result has already been adjusted according to this equation.

To verify the trueness of the comparison method, freshly frozen, human serum controls from NOKLUS with glucose concentrations at two levels were analysed. The NOKLUS-controls have target values determined with an isotope-dilution gas chromatography/mass spectrometry method at a Reference laboratory in Belgium; Laboratory for Analytical Chemistry, University of Gent, Belgium [8].
The agreement with target values from the reference laboratory in Belgium is shown in table 5.

Table 5. The comparison method – Control samples from NOKLUS's External Quality Assessment program, measured on the comparison method during the test period.

Control solution	Date	Target value from reference lab. in Belgium (mmol/L)	Mean value glucose (mmol/L)	n	CV % (95 % CI)	% deviation from target value
NOKLUS 1	7.10.2005	3,20	3,18	5	0,3 (0,2-0,8)	-0,7
NOKLUS 2	7.10.2005	7,78	7,74	5	0,5 (1,3-1,4)	-0,7

Discussion
The trueness of the comparison method is very satisfactory.

7.2. Precision and accuracy of FreeStyle

7.2.1. Precision of FreeStyle

All of the FreeStyle meters in the supplementary evaluation were checked by the biomedical laboratory scientists with the manufacturer's control solution. All of the results were inside the limits of the control.

All the results from the calculations of the precision are discussed at the end of this chapter.

Repeatability under standardised and optimal measuring conditions
The repeatability obtained under standardised and optimal conditions with capillary blood samples is shown in table 6. The table gives the results from the biomedical laboratory scientists' measurements. Raw data is shown in attachment 2.

Table 6. FreeStyle – Repeatability (results with patient samples) measured under standard and optimal conditions.

FreeStyle	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	3,5-15,4	8,6	23	0	3,5 (2,7-5,0)

Repeatability obtained by the diabetic patients
The repeatability obtained by the diabetic patients with capillary blood samples is shown in table 7. Raw data from the diabetic patients' measurements at NOKLUS is shown in attachment 3.

Table 7. FreeStyle – Repeatability (results with patient samples) measured by the diabetics.

FreeStyle	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Diabetics at NOKLUS	3,7-15,3	8,8	23	0	3,5 (2,7-5,0)

Reproducibility with Internal Quality Control
The results for reproducibility are obtained with the FreeStyle Control solution. The measurements are carried out on meter A during the whole evaluation period and at all the meters in use by the diabetic patients. All the control measurements are done by biomedical laboratory scientist. The control measurements on the diabetics' meters were done with the test strips distributed at the Noklus Centre at the consultation. The control solution was kept at NOKLUS Centre during the evaluation period.

The control solution was only measured five times at meter "A" during the evaluation. All measurements were inside the limit of the control solution. The reproducibility of FreeStyle at meter A is not calculated because of few results.
The reproducibility at all the meters of the diabetic patients is shown in table 8.
Raw data is shown in attachment 4.

Table 8. FreeStyle – Reproducibility (results with FreeStyle control solution) measured by the biomedical laboratory scientist on the diabetic patient's meters.

FreeStyle	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
The diabetic patient's meters	0517206	14,9-22,3	18,5	23	0	1,9 (1,5-2,7)

Discussion
The repeatability at FreeStyle is good when measured with capillary blood samples. The repeatability obtained under standardised and optimal conditions is somewhere between 2,7 and 5,0 % (meter A).
The repeatability obtained at NOKLUS by the diabetic patients is as good as the precision achieved by the biomedical laboratory scientists. The CV % is also between 2,7 and 5.

The reproducibility at the diabetics' meters measured with FreeStyle Control Solution was good. The CV was approximately 2 %.

7.2.2. Accuracy

To evaluate the accuracy of the results at FreeStyle, the agreement between FreeStyle and the comparison method is illustrated in two difference plots. The difference plots give a picture of both random and systematic deviation and reflect the total measuring error at FreeStyle. The total error is demonstrated for the first measurements of the paired results. Only one lot of test strips was used.
The limits in the plots are based upon the quality goals discussed in chapter 4 of this report. Under standardised and optimal measuring conditions the ISO-goal at 20 % is used. For the diabetic patients' self-measurements the "adjusted ISO-goal" at 25 % is used.

The accuracy, FreeStyle meter A, under standardised and optimal measuring conditions, with the first measurement is shown in figure 2.
The accuracy, FreeStyle, as measured by the diabetic patients with the first measurement is shown in figure 3. The raw data is shown in attachment 5.
The results from the two difference plots are summarised in table 10 and discussed afterwards.

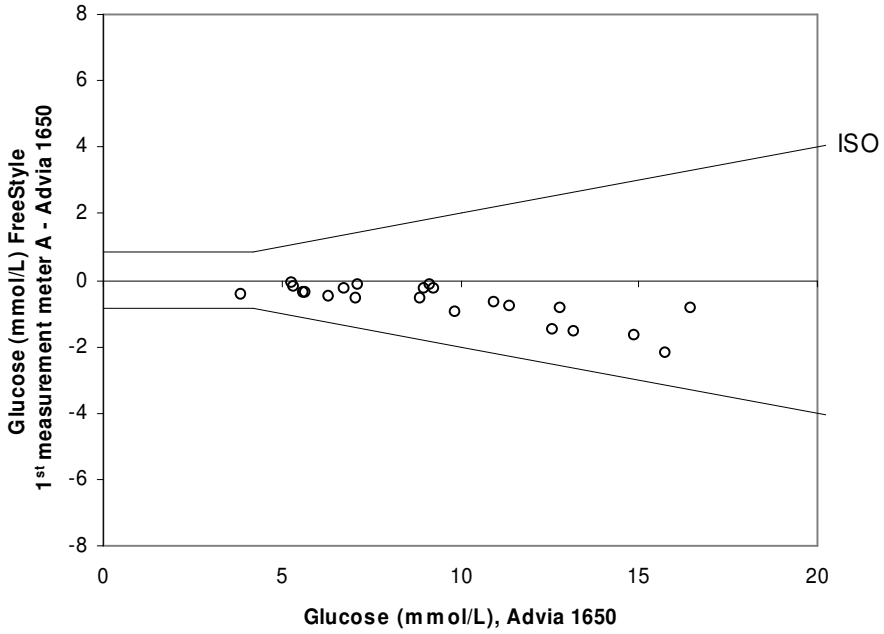

Figure 2. Accuracy. FreeStyle meter A (one lot of test strips) under standardised and optimal measuring conditions. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at FreeStyle and the mean value of the duplicate results at the comparison method. N = 22.

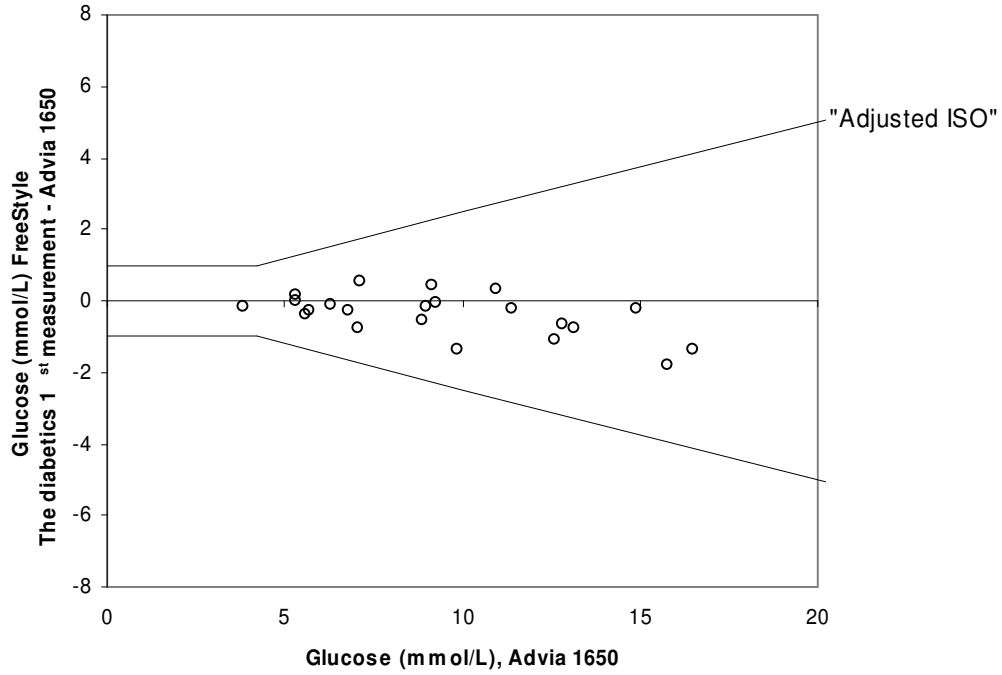

Figure 3. Accuracy. The diabetic patients' self-measurements. One lot of test strips.
The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at FreeStyle and the mean value of the duplicate results at the comparison method. N = 22.

Table 9. Total error of FreeStyle results compared to the reference method. Percentage FreeStyle results within the limits.

Measurements done by	n	Number of results (%)			Shown in figure
		< ADA (< ± 10 %)	**< ISO** < ± 20 % (and < ± 0,83 mmol/L at consentrations ≤ 4,2)	**< "adjusted ISO"** < ± 25 % (and < ± 1,0 mmol/L at consentrations ≤ 4,2)	
Biomedical laboratory scientist	22	77	100		2
Diabetic patients at NOKLUS	22	86	100	100	3

Discussion

Figure 2 shows that all the results obtained under standardised and optimal measuring conditions are within the ISO-limits. The summing up in table 9 shows that all the measurements are within the ISO-limits, but the results do not fulfil the strict limits recommended by ADA. Figure 3 shows that the diabetic patients' self-measurements fulfil the "adjusted ISO-goal". The results also fulfil the ISO-goal, as shown in table 9. The results do not fulfil the optimal quality goals from ADA.

Conclusion

The FreeStyle device fulfils the quality goals set in the ISO 15197 when used under standardised and optimal conditions. The quality goals are also met by the measurements of the diabetic patients. This conclusion is based on 22 results from finger samples.

8. References

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9. Attachments

1. Serial numbers, FreeStyle meters
2. Raw data, FreeStyle results under standardised conditions, meter A and B
3. Raw data, FreeStyle results, the diabetics measurements at NOKLUS
4. Raw data, internal quality control, FreeStyle
5. Raw data, Advia results, diabetic patients

Attachments with raw data are included only in the report to Abbott Norge AS.