# GlucoSure Plus

***A system for measurement of P—Glucose***
***manufactured by***
***Apex Biotechnology Corporation, Taiwan***

Report from an evaluation
organised by SKUP

Evaluated at the request of the general agent for Scandinavia
HaeMedic AB

SKUP/2004/38*

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**ATTACHMENTS**

1. Raw data. Patient sample results
2. Raw data. GlucoSure Plus internal quality control results
3. Raw data. NIST reference material results
4. Raw data. Internal quality control results for P—Glucose on Hitachi 917

The raw data attachments are included only in the report copy to HaeMedic AB.

# 1 Summary

The GlucoSure Plus measuring system (GlucoSure Plus) is intended for glucose measurements, both self-testing by diabetics and for use by health care personnel. GlucoSure Plus is manufactured by Apex Biotechnology Corporation, Taiwan. The general agent for Scandinavia is HaeMedic AB in Sweden.

The system is based on biosensor technology. To make a measurement, a GlucoSure Plus test strip is inserted into the GlucoSure Plus meter. The sample is drawn directly from a drop of blood on the patient's fingertip into test chamber on the test strip. The sample volume is 3 µL.
The meter displays the Plasma—Glucose result 10 seconds after a sample has been applied.
The measuring range is 1.7 — 30.6 mmol/L.

This evaluation is not a complete SKUP evaluation. Trained biomedical scientists carried out all the measurements on samples from adult diabetes patients. An evaluation how GlucoSure Plus performs in the hands of diabetics has not been performed.

The routine method for P—Glucose in the laboratory for clinical chemistry at the county hospital Norra Älvsborgs Lasarett (NÄL), Trollhättan, Sweden, was the designated comparison method in this evaluation. This is an accredited hexokinase method for glucose in plasma set up on a Roche Hitachi 917 instrument with reagents and calibrators from Roche.

**Results**
The imprecision was calculated from duplicate capillary samples from 102 adult diabetics.
The coefficient of variation (CV) was low, less than 4 % within the range 4.3 — 29.3 mmol/L.
Between-day imprecision was calculated from measurements of the manufacturer's water based control solutions. We found CV values between 4 and 11 %. Probably, these results do not reflect the real between-day imprecision, but rather indicate an unsuitability of the control solutions.

In the interval 4.6 — 12.0 mmol/L, the bias of GlucoSure Plus is negative, but small and of no clinical significance. In the interval above 12.0 mmol/L, the bias is positive (+0.89 mmol/L) but still acceptable.

According to the American Diabetes Association (ADA) the total error for measurements with new instruments for self-testing of diabetics should not exceed ±10 %. GlucoSure Plus does not fulfil this goal as only 81 of 103 or 79 % of the results were within the limits. The ADA goal can be seen as an optimal goal. ISO 15197:2003 "In vitro diagnostic test systems -- Requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus" gives the following minimum requirements: *95 % of the measurements must deviate less than ±20 % at level ≥4.2 mmol/L and less than ±0.83 mmol/L at level <4.2 mmol/L when compared with a reference method.* As 102 out of 103 or 99 % of the results are within these ISO tolerance limits, it is clear that GlucoSure Plus fulfils this quality requirement.

The opinions about the user-friendliness of GlucoSure Plus among the evaluating personnel is summarised by saying that the system is easy and rapid to use.

**Conclusion**
GlucoSure Plus can measure plasma glucose with low imprecision. The bias is negligible except for concentrations above 12 mmol/L, where a positive but acceptable bias was noted. The total errors are within the ISO requirements. The system is easy and rapid to operate. These good results with GlucoSure Plus are obtained when operated by biomedical scientists in the primary health care.

# 2 Planning of the evaluation

Scandinavian Evaluation of Laboratory Equipment for Primary Health Care, SKUP, has carried out an evaluation of GlucoSure Plus. The evaluation was first requested in 2002, when HaeMedic AB, the general agent in Scandinavia, had just started marketing GlucoSure Plus in Sweden. According to the manufacturer, the system is intended both for self-testing by diabetics and for use by professional health care personnel. In this SKUP evaluation trained and experienced biomedical scientists/laboratory technologists carried out measurements on samples from adult diabetics. It is desirable that this evaluation is supplemented with additional studies showing the performance when used by diabetics.

This evaluation follows the guidelines set out in a Norwegian evaluation guide [1], whose title in English will be: "Evaluation of analytic instruments — A guide especially dealing with evaluation of instruments for the primary health care." During the planning phase it was discussed which additional investigations beyond the SKUP model that might be necessary to create confidence in the system. The conclusion was that an investigation of between-meter variation should be carried out.

This evaluation thus comprised the following studies:

- Imprecision
- Between-day imprecision
- Bias
- Total error
- User friendliness
- Limited additional study of between-meter variation

Kemilaboratoriet (The Laboratory for Clinical Chemistry) at the county hospital Norra Älvsborgs Länssjukhus (NÄL), Trollhättan, Sweden, was appointed to have the responsibility for the evaluation. This laboratory is in this report called the NÄL laboratory. SKUP in Sweden, EQUALIS AB (External Quality Assurance in Laboratory Medicine in Sweden), HaeMedic AB and the NÄL laboratory entered into a contract. The practical work was done in the Laboratoriet (The Medical Laboratory) at Dalslands Sjukhus, Bäckefors, which is a local hospital nearby NÄL. This laboratory is in this report called the Dalslands Sjukhus laboratory. Both laboratories and several other laboratories co-operate within Enheten för laboratoriemedicin, NU-sjukvården (The Unit for Laboratory Medicine, NU Health Care). NU is an abbreviation for the organisation managing the co-operation between several hospitals among them the two county hospitals NÄL and Uddevalla Sjukhus.

This evaluation has been done in three steps. Initially a study was interrupted before SKUP had finished writing the report. Meanwhile, the precision of the system had been improved, and the contract parties agreed to restart the evaluation. After reviewing the preliminary results of the second evaluation in the spring 2004, the agent and the manufacturer together decided to recalibrate the GlucoSure Plus system. After this, the final evaluation started.

The first evaluation was discussed at a meeting in the Dalslands Sjukhus laboratory, 19 August 2002. The protocol and the practical planning of the evaluation were discussed.
The following persons participated at the meeting:
Lena Evaldsson, Biomedical Scientist, the Dalslands Sjukhus laboratory
Pernilla Jörgensen, Biomedical Scientist, the Dalslands Sjukhus laboratory

Märta Johansson, Medical Laboratory Technician, the Dalslands Sjukhus laboratory
Lars Ingvarsson, Managing Director, HaeMedic AB
Eivor Hellström, Instructor, the NÄL laboratory
Arne Mårtensson, Co-ordinator, SKUP Sweden, EQUALIS AB.

The final evaluation started with a meeting 20 April 2004 in the Dalslands Sjukhus laboratory. The following persons participated at that meeting:
Anne-Charlotte Torstensson, HaeMedic AB
Eivor Hellström, Instructor, the NÄL laboratory
Pernilla Jörgensen, Biomedical Scientist, the Dalslands Sjukhus laboratory
Eva Ungerberg-Andersson, Biomedical Scientist, the Dalslands Sjukhus laboratory
Lena Evaldsson, Biomedical Scientist, the Dalslands Sjukhus laboratory.

Eivor Hellström has instructed the staff in the Dalslands Sjukhus laboratory. Three biomedical scientists in the Dalslands Sjukhus laboratory did the blood sampling and the measurements with GlucoSure Plus on patient samples. The determinations with the comparison method were made in the NÄL laboratory.

Eivor Hellström and Arne Mårtensson have compiled this report.

# 3 Description of GlucoSure Plus

## 3.1 Facts about GlucoSure Plus

The GlucoSure Plus is manufactured by Apex Biotechnology Corporation, Taiwan.

The general agent for Scandinavia is:
HaeMedic AB
Företagargatan 18
SE-266 32 Munka Ljungby
Sweden
Phone: +46 (0)431 43 20 30
Fax: +46 (0)431 43 00 30.
E-mail: lars.i@haemedic.se

The GlucoSure Plus measuring system consists of the GlucoSure Plus test strip and the GlucoSure Plus meter. Some basic facts about the system are shown in table 1.

**Table 1. Excerpts from specifications in the manual**

| | |
|---|---|
| Test strips: | GlucoSure Plus test strips<br>(2 x 25 test strips per package) |
| Sample volume: | Approximately 3 µL capillary blood |
| Measurement duration: | 10 seconds |
| Concentration range: | 1.7 — 30.6 mmol/L |
| Power supply: | 1 piece, 3 V, lithium battery |
| Display: | Liquid crystal display (LCD) |
| Allowed ambient temperature: | +18 — +38 ºC |
| Allowed ambient humidity: | <85 % relative humidity |
| Memory capacity: | 10 latest test results |
| Allowed haematocrit range: | 30 — 55 % |
| Meter size: | 100 x 58 x 21 mm |
| Meter weight: | 64 g |

To make a measurement, a test strip is inserted into the meter. The side of the outer end of the strip is used to draw the sample directly from a drop of blood on the patient's fingertip. The test chamber on the test strip is filled with 3 µL blood. A beep signal is heard when the test chamber has been filled. The meter displays a quantitative result 10 seconds after the sample was applied. The measuring range is 1.7 — 30.6 mmol/L.

The measuring system is based on biosensor technology. In the test strip the oxidation of glucose is catalysed by the enzyme glucose oxidase. This reaction is further coupled through a series of redox reactions through which electrons are finally delivered to the electrode surface on the test

strip in proportion to the glucose concentration in the sample. The generated current is measured in the GlucoSure Plus meter.

GlucoSure Plus is calibrated against a plasma calibrated whole blood method, YSI (Yellow Springs Instrument Co). The results produced are Plasma—Glucose values and not Blood—Glucose values. Before a new package of test strips can be used a new code card for calibration must be inserted into the meter.

A control test strip is used to test the function of the meter. To test the function of the complete system, i.e. both meter and test strips, the manufacturer supplies control solutions with low and high glucose levels. These control solutions are stable about one month.

## 3.2 Picture of GlucoSure Plus


The picture shows the meter with the inserted test strip in approximately real size.

# 4 Materials and methods

## 4.1 The designated comparison method

The routine method for Plasma—Glucose in the NÄL laboratory was the designated comparison method in this evaluation. This is a hexokinase method. The reagent is Gluco-quant® Glucose/HK, supplied by Roche Diagnostics GmbH.

The method is implemented on two Hitachi 917 instruments, also supplied by Roche. The set-up is completely according to the instructions from Roche. The reaction runs at 37 ºC. The sample volume is 10.0 µL.

In the first reaction step, hexokinase catalyses the conversion of glucose to glucose-6-phosphate as shown:

$$\text{glucose} + \text{ATP} \xleftrightarrow{\text{hexokinase}} \text{glucose-6-phosphate} + \text{ADP}$$

Then Glucose-6-phosphate dehydrogenase (G-6-PDH) catalyses the oxidation of glucose 6-phosphate as shown in the following reaction:

$$\text{glucose-6-Phosphate} + NADP^{+} \xleftrightarrow{\text{G-6-PDH}} \text{gluconate-6-phosphate} + NADPH + H^{+}$$

NADPH is formed at a speed that is directly proportional to the glucose concentration in the sample. NADPH is measured photometrically at 340 nm.

The comparison method is accredited. There are two Hitachi 917 instruments in the NÄL laboratory. Only one of the instruments was used in the evaluation, namely the instrument called ”Ettan”.

The comparison method was calibrated with “Calibrator for automated systems / Cfas” supplied by Roche. The calibrator is lyophilised and was re-dissolved at the laboratory.

## 4.1.1 Validation of the comparison method

### 4.1.1.1 Correction of the comparison method results

During the evaluation period the laboratory staff made no changes of the method set up or changes of reagent batches.

The comparison method is checked by frequent measurements of internal quality control samples. "Liquid Unassayed Multiqual", from BioRad, has been used for this purpose.

When the internal quality results for the comparison method on Hitachi 917 were examined closer, a shift in the concentration level became evident. The mean value of the control was higher after the morning of 07 October 2004. The results differed on average by 2.7 %.
See table 2.

**Table 2. Internal quality control results with the comparison method**

| Dates | Number of results | P—Glucose, found average value / set value (%) | Difference (%) |
|---|---|---|---|
| 28-Aug-04 — 7-Oct-04 | 287 | 98.0 | |
| 7-Oct-04 — 19-Oct-04 | 75 | 100.7 | +2.74 |

After this observation it was confirmed that the comparison method had actually been recalibrated once during the evaluation period and that this recalibration was done 7 am 07 October 2004. We therefore decided to adjust the results from the comparison method as if the method had not been re-calibrated during the evaluation. Thus, all results with the comparison method produced since the morning of 07 October 2004, are multiplied with the correction factor 0.973. All presentations and calculations of comparison method results except the raw data attachments and table 2 above, has been preceded by this correction.

#### 4.1.1.2 Imprecision of the comparison method

In table 3, the imprecision results of the comparison method during the evaluation period are presented. From each patient there was one sample collected for the comparison method. On each of these samples there was one duplicate determination done. The imprecision of the comparison method is calculated on these duplicate results.

**Table 3. Imprecision of the comparison method. Capillary patient samples**

| Level[#] | P—Glucose Interval (mmol/L) | Excluded results* | P—Glucose Average value (mmol/L) | n | CV (%) (95 % confidence interval) |
|---|---|---|---|---|---|
| Low | 4.3 — 6.9 | 0 | 6.0 | 34 | 1.1 (0.9 — 1.5) |
| Medium | 7.0 — 11.9 | 0 | 9.2 | 36 | 1.3 (1.0 — 1.6) |
| High | 12.0 — 29.3 | 0 | 15.2 | 33 | 1.2 (1.0 — 1.6) |
| All | 4.3 — 29.3 | 0 | 10.0 | 103 | 1.3 (1.1 — 1.5) |

[#] The results are divided into concentration subgroups according to the GlucoSure Plus results to enable a comparison between table 3 and table 8. The latter contains the corresponding GlucoSure Plus results. Note: The calculated imprecision values are of different kind in the two tables; for the comparison method in table 3 it is calculated from duplicate determinations on the same sample and for GlucoSure Plus in table 8 it is calculated from determinations of duplicate samples from the same finger puncture.

* Please refer to the text in section 4.2.1.5 about applied test for exclusion of results.

#### 4.1.1.3 Internal quality control for the comparison method

Table 4 contains the internal quality results obtained with the comparison method during the evaluation period. The Level 1 control sample has typically been measured twice per day and the Level 2 four times per day. The assigned values are of minor importance because they are just set locally by the NÄL laboratory from historical data. Change of operator, change of zero-calibration, change of reagent bottles and change of measurement day during the evaluation period has influenced the imprecision figures in the table.

**Table 4. Comparison method results on internal quality control samples**

| Quality control material | P—Glucose | | | n | CV % (95 % conf. interval) |
|---|---|---|---|---|---|
| | Assigned value (mmol/L) | Found average (mmol/L) | Found/Assigned value (%) | | |
| BioRad, Multiqual Level 1 | 3.37 | 3.32 | 98.4 | 123 | 1.6 (1.4 — 1.8) |
| BioRad, Multiqual Level 2 | 6.59 | 6.55 | 99.4 | 239 | 1.5 (1.4 — 1.7) |

#### 4.1.1.4 External quality assurance results for the comparison method

The NÄL laboratory participates in an external quality assurance programme supplied by Labquality, Helsinki, Finland. The laboratory's results in that programme are shown in table 5. The result in each row derives from triplicate determinations on a single sample each month. The matrix of the control samples varies. Commercial liquid human serum was used in August and October. Commercial lyophilised human serum was used in July and September.

The results from a participant in the programme are primarily compared with results from similar methods. The results from similar methods are presented in the same method group. The P—Glucose results from the NÄL laboratory are compared with the results from other photometric laboratory methods using glucose oxidase, hexokinase or glucose dehydrogenase reagents. The target interval given by Labquality is calculated from the average method group result ±6 %. Bias for the comparison method is calculated relative to the average method group result.

**Table 5. Comparison method results in an external quality assurance programme**

| Time period | Method group | | | | The comparison method | |
|---|---|---|---|---|---|---|
| | Average P—Glucose (mmol/L) | Number of laboratories | Repro-ducibility CV (%) | Target interval P—Glucose (mmol/L) | Found P—Glucose (mmol/L) | Bias (%) |
| July 2004 | 2.65 | 373 | 6.0 | 2.49 — 2.81 | 2.6 | –1.9 |
| Aug. 2004 | 10.43 | 381 | 3.6 | 9.80 — 11.05 | 10.4 | –0.3 |
| Sept. 2004 | 4.53 | 392 | 4.3 | 4.26 — 4.80 | 4.3 | –5.1 |
| Oct. 2004 | 9.43 | 381 | 3.5 | 8.87 — 10.00 | 9.4 | –0.3 |

#### 4.1.1.5 Results of the comparison method on certified reference materials

An important part of the validation of the comparison method is measurements on certified reference materials. "SRM 965a" from National Institute of Standards and Technology (NIST) was measured before, during and after the evaluation at five different days. These NIST materials are frozen human sera at four levels. The measurement results on the NIST materials are summarised in table 6. The confidence intervals for the found averages have been calculated by the statistical ANOVA method.

**Table 6. Results of the comparison method on certified reference material**

| Reference material | P—Glucose | | | | |
|---|---|---|---|---|---|
| | Assigned value (mmol/L) | Found average (95 % conf. interval) (mmol/L) | n | CV % (95 % conf. interval) | Found average relative Assigned value (%) |
| NIST SRM 965a | 1.918 ±0.020 | 1.951 ±0.042 | 30 | 1.5 (1.2 — 2.0) | 101.7 |
| | 4.357 ±0.073 | 4.355 ±0.176 | 30 | 2.1 (1.7 — 2.9) | 100.0 |
| | 6.777 ±0.048 | 6.868 ±0.191 | 30 | 1.6 (1.3 — 2.2) | 101.3 |
| | 16.24 ±0.19 | 16.32 ±0.44 | 29 | 1.2 (0.9 — 1.6) | 100.5 |

#### 4.1.1.6 Discussion of the validation of the comparison method

The imprecision results of the comparison method were low. The CV, calculated from the duplicate measurements on patient samples and from the internal quality control results, was about 1.5 %.

The external quality assurance programme results show that the comparison method produce similar results as other laboratories in Scandinavia. On the certified reference materials from NIST the comparison method results show a small positive bias of approximately 1 %. This positive deviation might be counteracted by a small decrease of the P—Glucose concentration due to glycolysis in the patient samples during the pre-analytical phase for the comparison method. This source of errors is observed with all Plasma—Glucose methods when samples are not measured immediately. As this bias arises in the patient samples during the pre-analytical phase it is impossible to check it by measuring certified reference materials.

In this evaluation, plasma was separated from the blood cells within 20 minutes after the sample collection. According to Chan [2] the P—Glucose concentration in samples collected in fluoride tubes may decrease about 0.13 mmol/L during the first 30 minutes after sampling. Savolainen [3] has reported a decrease of about 0.28 mmol/L during the first hour after sampling. de Pasqua et al. [4] show that the P—Glucose concentration in separated plasma is stable at least 24 hours. Considering these literature findings, it is likely that the concentration has decreased about 0.1 mmol/L or on average 1 % before measurements with the comparison method in our evaluation.

We have accordingly chosen to not correct for the small bias noticed with the reference materials.

## 4.2 Evaluation procedure

### 4.2.1 Evaluation in a primary care laboratory

According to the SKUP model for evaluations of equipment for the primary care, the evaluation should be done both in a hospital laboratory by experienced biomedical scientists and in at least two primary care centres, often by primary care personnel with limited laboratory education. The evaluation of GlucoSure Plus was done only in one small local hospital laboratory and is, therefore, not a complete SKUP evaluation. The laboratory is serving both primary care and the small local hospital and is organised like the big primary care centres in Sweden. In this case three biomedical scientists performed the measurements. GlucoSure Plus is intended both for use by health care personnel and for self-testing by diabetics. How the system performs in the hands of diabetics is not evaluated.

#### 4.2.1.1 Blood sampling

For the investigation of the imprecision of GlucoSure Plus and for the comparison with the comparison method, capillary samples from 103 adult diabetics were taken. These patients had been referred to the laboratory at the local hospital, Dalslands Sjukhus, for measurement of P—Glucose with the routine method, HemoCue, during the time period 28 August — 19 October 2004. Patients were verbally informed about the study and confirmed their consent in writing.

After capillary puncture the first blood drop was wiped off and samples for the different P—Glucose determinations were taken in the following order:

1. Routine method
2/4. GlucoSure Plus
3. GlucoSure Plus
4/2. Comparison method

For every second patient the comparison method sample was taken before the GlucoSure Plus samples. The samples for GlucoSure Plus were drawn directly into the test strip for immediate measurements.

The capillary punctures were made by lancets supplied by HaeMedic AB.

The capillary samples for the comparison method were collected in micro tubes containing the additives sodium fluoride and disodium-EDTA.

We tried to take all the samples from each patient from one and the same capillary puncture. For nine patients out of 103 this was not possible — another puncture was done to collect the comparison method sample. Following each sampling, remaining blood was wiped off before a new sample was drawn. Three biomedical scientists working in the laboratory at Dalslands Sjukhus performed the sampling.

The measurements with GlucoSure Plus were carried out according to the instructions in the manual. Only one lot of test strips was used for all measurements in the evaluation.

Five GlucoSure Plus meters were used in the evaluation. The measurements were alternated between the five meters. The first duplicate was measured on meter number 1, the second duplicate on meter no.2, …, the sixth duplicate on meter no. 1 and so on.

The Microtainer tube was centrifuged directly after the sample collection at 13 000 rpm and radius 8.5 cm, that is 16 000 G, in 2 minutes. 130 – 150 µL plasma was transferred from the Microtainer tube to another tube within 20 minutes from the sample collection.

#### 4.2.1.2 Internal quality control of GlucoSure Plus

The control test strip and control solutions at two levels were measured daily during the evaluation.

#### 4.2.1.3 Sample storage and transport

The plasma samples for the comparison method were stored in refrigerator temperatures at Dalslands Sjukhus and during transport. The samples were sent to the NÄL laboratory not later than 24 h after the sample collection.

#### 4.2.1.4 Comparison method measurements

When the samples arrived at the NÄL laboratory they were analysed immediately. All samples were analysed within 30 hours after being drawn.

#### 4.2.1.5 Treatment of raw data

The tables in the attachments contain all raw data from the evaluation.

According to the SKUP model, an initial result is never replaced by a re-analysed result. However, the results are tested for outliers according to Burnett [5], and any outlier is excluded from the statistical calculations.

Before the calculation of imprecision, Burnett's rule has been applied to the differences between the results of duplicate determinations. First, preliminary mean value and SD are calculated for all differences within a level group. If any difference differs by more than approximately ±3 SD from the mean of all differences in the level group that duplicate pair is excluded. In a similar way, before calculation of bias, Burnett's rule has been applied to the differences between the tested method and the comparison method. The numbers of excluded results are presented in the tables.

The exact numbers of standard deviations for exclusion varies depending on the number of values the calculation is carried out for. For instance, for n = 20, the limit is set at ±3.02 SD, for n = 30 at ±3.14 SD, and for n = 100 at ±3.47 SD. According to Burnett, the outlier test is repeated in the necessary number of steps until no value differs more than allowed.

## 4.2.2 Products details

### 4.2.2.1 The blood sampling

The capillary punctures were made by lancets supplied by HaeMedic AB, Box 116, SE-226 21 Munka Ljungby, Sweden:
Hemolance Plus, yellow, Product no: 51316. Lot no. 2-26-408.

The capillary samples for the comparison method were collected in micro tubes, BD Microtainer™ Capillary Blood Tube, glucose tube, additives: sodium fluoride and disodium-EDTA, draw volume: 400 — 600 µL, grey Microgard™ closure. Product no: 365993. Lot no. 3267751. Supplied by BD, 1 Becton Drive, Franklin Lakes, NJ 07417, USA.

### 4.2.2.2 The comparison method

The used reagent was Gluco-quant® Glucose/HK, supplied by Roche Diagnostics GmbH, Mannheim, Germany, catalogue number 1876899, lot nr 654731.

The used calibrator was "Calibrator for automated systems / Cfas" supplied by Roche, catalogue number 759350, lot number 160766.

As internal quality control samples for the comparison method "Liquid Unassayed Multiqual", lyophilised control serum from BioRad, US, has been used.
Level 1, Cat No 983000, Lot no: 39490 and 39491.
Level 2, Cat No 984000, Lot no: 39492.

### 4.2.2.3 GlucoSure Plus

The lot number of test strips used for the measurements in the evaluation was NS 128J.

Five GlucoSure Plus meters used in the evaluation had the following serial numbers:
Hm 50014099 (meter no. 1)
Hm 50014100 (meter no. 2)
Hm 50014103 (meter no. 3)
Hm 50014162 (meter no. 4)
Hm 50014170 (meter no. 5)

The control solutions used for GlucoSure Plus during the evaluation had the following names and batch numbers:
Contrex, Level 1 batch nr TC 930105M and
Contrex, Level 2 batch nr TC 930105H.

# 5 Analytical quality goals

There are different criteria for setting quality specifications for analytical methods. Ideally the quality goals should be set according to the medical requirements 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. GlucoSure Plus is designed for monitoring diabetes, and the quality goals must be set according to this.

A recognised way to set quality goals is to base the goals on the biological variation for the compound [6, 7]. Information regarding the biological variation for most compounds is found in different databases, for example Westgard [8].

For systems designed for monitoring diabetes one should point out the need of a method with good precision [9]. According to the American Diabetes Association (ADA), the total error for systems designed for self monitoring and point of care testing of glucose should not exceed 10 % in the range 1.67 — 22.2 mmol/L [10]. The quality goal from ADA could be seen as an optimal and seldom achieved goal for the analytical quality of these systems. According to ADA, the imprecision of new glucose devices must be less than 5 %. Other authors also recommend an imprecision of 5 % or less [11].

A quality requirement for the total error is specified in the standard ISO 15197:2003 "In vitro diagnostic test systems -- Requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus" [12]. This ISO standard is an international protocol for evaluating systems designed for self-measurements of blood glucose. This is a quality requirement for measurements by trained laboratory staff and thus applicable in this evaluation.

ISO 15197 sets out the following minimum requirements:

*95 % of the measurements must deviate less than ±20 % at level ≥4.2 mmol/L*
*and less than ±0.83 mmol/l at level <4.2 mmol/L when compared with a reference method.*

Ideally, the same quality goals should apply for measurements performed by diabetic patients. Previous investigations in the NOKLUS project "Diabetes-Self-measurements" and results from evaluations under the direction of SKUP, have shown that it has been difficult to attain these quality requirements for most of the self-monitoring glucose systems when the diabetic patients performed the measurements.

# 6 Results and discussion

## 6.1 Evaluation in a primary care laboratory

### 6.1.1 Exclusion of results

The measurement results were first sorted into three level groups according to the first result on GlucoSure Plus. The outlier test described in Section 4.2.1.5 was then applied to the data at each level group separately. The following differences were tested for outliers:

- The differences between the two measurements with GlucoSure Plus.
- The differences between the two measurements with the comparison method.
- The differences between the mean value of the two measurements with GlucoSure Plus and the mean value of the two measurements with the comparison method.

Totally there were 103 patient results. Only one result was excluded as an outlier. The excluded result and the reason for the exclusion are shown in table 7.

**Table 7. Excluded result**

| Sample no. | P—Glucose (mmol/L) | | | | | | | Reason for exclusion |
|---|---|---|---|---|---|---|---|---|
| | GlucoSure Plus | | | Comparison method | | | Difference GlucoSure Plus – Comp.method | |
| | 1 | 2 | Mean | 1 | 2 | Mean | | |
| 89 | 6.6 | 5.0 | 5.80 | 5.85 | 5.85 | 5.85 | –0.05 | GSP 1 ≠ GSP 2 |

Reason for exclusion explained:
GSP 1 ≠ GSP 2 — Statistically too big difference between the two GlucoSure Plus results

The scope of the calculations of imprecision and bias is to give measures valid for representative patient results. The outlier result above is thus excluded, leaving 102 results in the calculations of imprecision and bias.

The total error diagram, on the other hand, should show both systematic and random errors. The outlier result above is therefore included in the diagram, and all 103 results are shown in the diagram.

## 6.1.2 Imprecision

### 6.1.2.1 Imprecision of patient samples

The imprecision values of GlucoSure Plus on patient sample results are presented in table 8. From each patient's finger, two capillary samples were drawn directly into the GlucoSure Plus test strips. The calculations are made on these duplicate results. Three operators performed the measurements and five meters were used during the evaluation period and this has influenced the calculated imprecision values.

**Table 8. Imprecision of GlucoSure Plus. Capillary patient samples**

| Level | P—Glucose interval (mmol/L) | Excluded results* | P—Glucose Average value (mmol/L) | n | CV (%) (95 % confidence interval) |
|---|---|---|---|---|---|
| Low | 4.3 — 6.9 | 1 | 5.9 | 33 | 3.8 (3.0 — 5.0) |
| Medium | 7.0 — 11.9 | 0 | 8.9 | 36 | 3.1 (2.5 — 4.1) |
| High | 12.0 — 29.3 | 0 | 15.8 | 33 | 3.2 (2.6 — 4.3) |
| All | 4.3 — 29.3 | 1 | 10.1 | 102 | 3.5 (3.1 — 4.1) |

* Please refer to the text in 6.1.1 for explanation of excluded result.

### 6.1.2.2 Internal quality control results

Following the manual, the electronics of the meters were checked every day during the evaluation. An approved test is indicated by a symbol (a happy face) on the meter display. All checks performed during the evaluation were OK.

Internal quality control solutions were measured daily at each of the five GlucoSure Plus meters used during the evaluation days. From the data the between-day imprecision values were calculated. See table 9.

**Table 9. Between-day imprecision* with GlucoSure Plus control solutions**

| Assigned intervals (mmol/L) | Meter no | Found intervals (mmol/L) | n | Mean values (mmol/L) | CV (%)* (95 % confidence interval ) |
|---|---|---|---|---|---|
| Level 1 3.8 — 5.6 | 1 | 3.8 — 5.0 | 17 | 4.3 | 9.1 (6.8 — 13.8) |
| | 2 | 3.8 — 5.5 | 17 | 4.3 | 10.5 (7.8 — 15.9) |
| | 3 | 3.8 — 5.2 | 17 | 4.5 | 10.3 (7.7 — 15.7) |
| | 4 | 3.9 — 5.4 | 17 | 4.5 | 10.0 (7.5 — 15.3) |
| | 5 | 3.8 — 5.3 | 17 | 4.5 | 9.8 (7.3 — 15.0) |
| | 1 — 5 | 3.8 — 5.5 | 85 | 4.4 | 10.1 (8.7 — 11.8) |
| | | | | | |
| Level 2 9.1 — 13.7 | 1 | 10.2 — 12.2 | 17 | 11.1 | 5.4 (4.0 — 8.2) |
| | 2 | 10.8 — 12.6 | 17 | 11.7 | 4.7 (3.5 — 7.2) |
| | 3 | 10.3 — 12.4 | 17 | 11.6 | 4.4 (3.2 — 6.6) |
| | 4 | 10.8 — 12.7 | 17 | 11.7 | 4.4 (3.2 — 6.6) |
| | 5 | 10.8 — 12.7 | 17 | 11.7 | 4.6 (3.4 — 6.9) |
| | 1 — 5 | 10.2 — 12.7 | 85 | 11.6 | 4.9 (4.3 — 5.8) |

* The CV values for between-day imprecision in this table include the within-series imprecision.

### 6.1.2.3 Discussion of the imprecision of GlucoSure Plus

The imprecision calculated on patient samples was low. The CV was <4 % within the interval 4.3 — 29.3 mmol/L.

The between-day imprecision was calculated from measurements of the manufacturer's water-based control solutions. All of the obtained results were within the manufacturer's target intervals. Compared to the results of blood samples, the results of the control solutions show a considerably higher imprecision with CVs between 4 and 11 %. Probably the results of control solutions do not reflect the measurement quality of the patient samples and thus the control solutions are not so suitable for the purpose to check the measurement quality. Please note that the glucose concentration of level 1 is low. This contributes to the high CV values.

### 6.1.3 Bias

Bias was calculated from determinations on 103 capillary samples from adult diabetics.
The means of the duplicate sample results with GlucoSure Plus are compared with the means of the duplicate determinations with the comparison method. The result is shown in table 10.

**Table 10. Bias of GlucoSure Plus results. Capillary patient samples in the primary care laboratory**

| Level group | P—Glucose interval (mmol/L) | Excluded results* | Average P—Glucose (mmol/L) | n | Bias (95 % confidence interval) (mmol/L) |
|---|---|---|---|---|---|
| Low | 4.55 — 6.99 | 1 | 5.89 | 34 | –0.14 (–0.29 — +0.01) |
| Medium | 7.00 — 11.99 | 0 | 9.08 | 36 | –0.27 (–0.48 — –0.07) |
| High | 12.00 — 29.00 | 0 | 16.05 | 32 | +0.89 (+0.48 — +1.30) |

* Please refer to the text in 6.1.1 for explanation of the excluded result.

#### 6.1.3.1 Discussion of the bias of GlucoSure Plus

In the interval 4.6 — 12.0 mmol/L, the bias of GlucoSure Plus is small. This small bias has no clinical consequences. Above 12.0 mmol/L, the bias is positive, +0.89 mmol/L, but the size of this bias is acceptable.

As can be seen from the total error diagram (Fig 1), the bias does not turn positive exactly at 12.0 mmol/L. As only two results are above 20 mmol/L, it is not possible to judge the bias for higher glucose concentrations from this evaluation.

### 6.1.4 Total error

The agreement between GlucoSure Plus and the comparison method is illustrated in a difference diagram, figure 1. In the diagram the x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the deviation of the first measurement on GlucoSure Plus from the mean value of the duplicate results of the comparison method. The difference diagram gives a picture of both random and systematic deviations and reflects the total error of GlucoSure Plus.

The limits in the diagram are based upon the quality goals discussed in a previous chapter of this report.

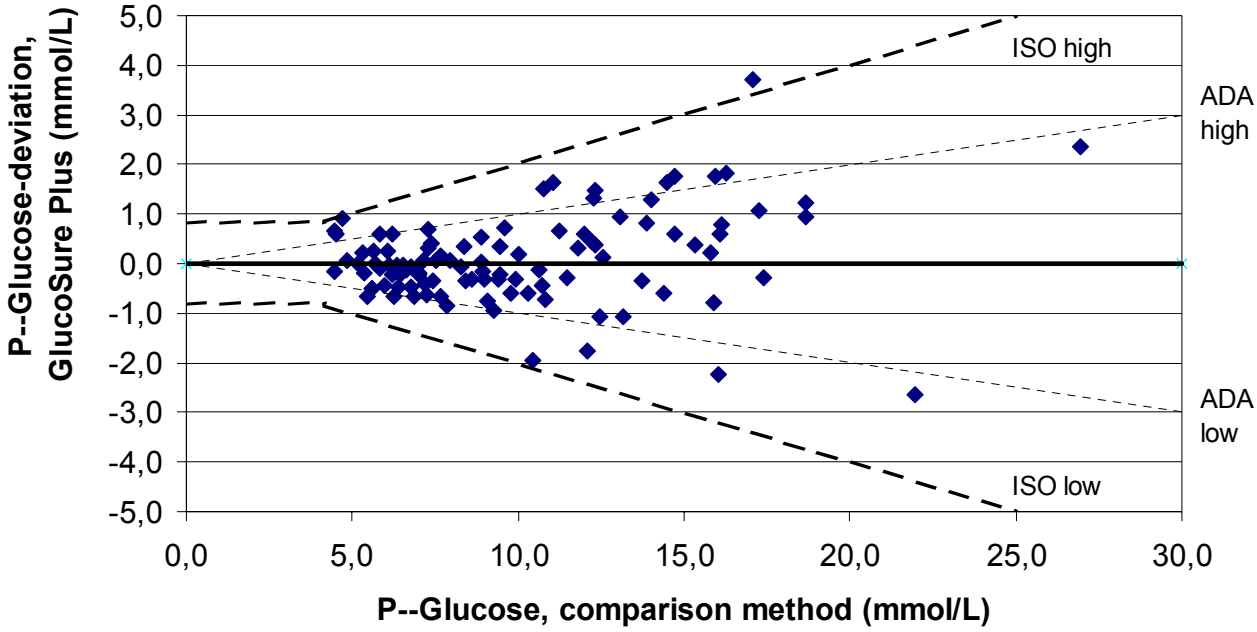


**Figure 1. Total error diagram**
The deviations of the GlucoSure Plus results from the comparison method results are shown for 103 patient samples. No outlier excluded.
Thin stippled lines represent tolerance limits according to the American Diabetes Association (ADA).
Bold stippled lines represent tolerance limits according to the ISO 15197:2003 [12].

#### 6.1.4.1 Proportion of results within given deviation limits

In Table 11 the deviation of single results with GlucoSure Plus are presented as proposed in the ISO 15197 standard.

**Table 11. Proportion of GlucoSure results ≥4.2 mmol/L within given deviation limits**

| Within ±5 % | Within ±10 % | Within ±15 % | Within ±20 % |
|---|---|---|---|
| 53/103 (51 %) | 81/103 (79 %) | 101/103 (98 %) | 102/103 (99 %) |

#### 6.1.4.2 Discussion of the total error for GlucoSure Plus results

According to ADA the total error for systems designed for self monitoring and point of care testing of glucose should not exceed 10 % in the range 1,67 — 22,2 mmol/L [10]. The quality goal from ADA could be seen as an optimal goal for the analytical quality for these systems. GlucoSure Plus does not fulfil the ADA quality goal for the total error as only 81 out of 103 or 79 % of the results are inside the limits. According to ADA the imprecision of new glucose devices must be less than 5 %. GlucoSure Plus fulfils this ADA quality goal for imprecision.

ISO 15197:2003 [12] gives the following minimum requirements: *95 % of the measurements must deviate less than ±20 % at level ≥4.2 mmol/L and less than ±0.83 mmol/L at level <4.2 mmol/L when compared with a reference method.* As 102 out of 103 or 99 % of the results are inside these ISO tolerance limits, it is clear that GlucoSure Plus fulfils this quality requirement.

## 6.1.5 Differences between different meters

### 6.1.5.1 The imprecision with different meters

The imprecision has been calculated for each of the five GlucoSure Plus meters that were used in the evaluation. See table 12. Note that the calculation for each meter is not done on the same samples so the differences in average P—Glucose have no importance.

**Table 12. Imprecision of five GlucoSure Plus meters**

| Meter no. | Average P—Glucose (mmol/L) | n | CV % (95 % confidence interval) |
|---|---|---|---|
| 1 | 9.9 | 21 | 3.3 (2.5 — 4.7) |
| 2 | 9.7 | 21 | 4.0 (3.1 — 5.8) |
| 3 | 9.8 | 21 | 3.7 (2.9 — 5.4) |
| 4 | 10.9 | 19 | 3.8 (2.9 — 5.6) |
| 5 | 10.8 | 20 | 2.7 (2.0 — 3.9) |

### 6.1.5.2 The bias with different meters

The bias has been calculated for each of the five GlucoSure Plus meters that were used in this evaluation. See table 13. As shown in the bias calculation in chapter 5.1.3, a small negative bias was noticed for P—Glucose results below 12.0 mmol/L and a positive bias above that level. The bias values for each meter are shown at the two levels separately.

**Table 13. Bias for five GlucoSure Plus meters at two P—Glucose levels.**

| Meter no | P—Glucose (GlucoSure Plus) (mmol/L) | n | Bias (95 % Confidence Interval) (mmol/L) |
|---|---|---|---|
| 1 | <12.0 | 15 | –0.3 (–0.5 — +0.0) |
| 2 | <12.0 | 13 | –0.3 (–0.7 — +0.2) |
| 3 | <12.0 | 17 | –0.1 (–0.3 — +0.1) |
| 4 | <12.0 | 12 | –0.1 (–0.5 — +0.3) |
| 5 | <12.0 | 22 | +0.1 (–0.4 — +0.6) |
| 1 | ≥12.0 | 6 | +0.6 (–0.8 — +2.1) |
| 2 | ≥12.0 | 8 | +1.1 (+0.6 — +1.6) |
| 3 | ≥12.0 | 4 | +0.6 (–0.8 — +2.1) |
| 4 | ≥12.0 | 7 | +0.9 (–0.7 — +2.4) |
| 5 | ≥12.0 | 7 | +1.1 (+0.1 — +2.0) |

#### 6.1.5.3 Discussion of the differences between different meters

This part of the evaluation is an additional investigation not included in the standard protocol for a SKUP evaluation. In some of the other SKUP evaluations more comprehensive investigations of the between-meter variation have been performed. To do such investigations it is a condition that the same samples are measured with several meters. The investigation method used in this evaluation is less complicated but not so sensitive to detect differences between the meters.

The confidence intervals for both imprecision and bias values for the different meters are overlapping. With this limited number of results, we could not detect any statistically significant differences between the meters. The conclusion is that there are no big differences in imprecision or bias values for the five meters used in this evaluation.

## 6.1.6 Evaluation of the user friendliness

### 6.1.6.1 Questionnaire

The biomedical scientists at Dalslands Sjukhus filled out a questionnaire about the user manual and the user-friendliness of GlucoSure Plus at the end of the evaluation period. Eivor Hellström at NÄL first modified the questionnaire from a SKUP original. The opinions expressed in the questionnaire are presented below.

Positive opinions:

- The immediate impression of GlucoSure Plus is that the meter is easy and handy to use. It is easy to insert the test strip into the meter and to draw blood into the test strip at least with a big drop of blood on the sampling site.
- The overall opinion about the manual is that it is good. It is clear, there is no missing information and there is no superfluous information.
- It is possible to work with the system in a hygienic way and GlucoSure Plus is quick to show the measurement result. The results are clearly shown in the display window.

Negative opinions:

- The GlucoSure Plus beep signal sometimes might sound before the test chamber on the test strip is completely filled. See more about this below.
- If the blood is drawn into the test strip before the drop symbol is shown, you may get a false too low measurement result. The manual informs about this but it could be emphasised even more.
- Two pages in the manual describe how to do a measurement. This part is a bit disorganized and could be clearer.
- It is easy to calibrate the meter but a little sluggish to exchange the code strip.

During the evaluation it came to our knowledge that a conceivable buyer of GlucoSure Plus suspected that the GlucoSure Plus beep signal sometimes might sound before the test chamber on the test strip is completely filled. The persons engaged in this SKUP evaluation never experienced such problems.

The laboratory at Dalslands Sjukhus investigated how the GlucoSure Plus behaved with intentionally incompletely filled test chambers. The test chambers on four test strips were filled to different extent with an internal quality control blood sample. The HemoCue result for this control sample was 10.9 mmol/L.

1. Less than half test chamber filled. Result: LO
2. Half filled test chamber. Result: 6.2 mmol/L
3. Completely filled test chamber from a small drop. Result: 11.2 mmol/L
4. Completely filled test chamber from a big drop. Result: 10.7 mmol/L

This small experiment thus shows that when the test chamber is not full, it is possible to achieve a “LO” or a false too low result. The beep signal sounded in all the four cases above, which means twice when the test chamber was about half-full. As the test chamber is very easy to fill with the necessary volume of blood, the risk of insufficiently filled test chambers in practice is small.

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